PROCEEDINGS

of the

ROYAL

SOCIETY OF MEDICINE

Section of Pædiatrics

President—G. H. MACNAB, M.B., F.R.C.S.

[*November* 26, 1954]

Neonatal Hepatitis.—S. D. V. WELLER, M.D., M.R.C.P.

Anne P., born 21.12.51. First child. Parents healthy, but mother had a non-toxic goitre of long standing. Normal pregnancy and delivery.

Present illness.—Physiological jaundice cleared at 7 days. Weight gain satisfactory till 3 weeks. Multiple hæmorrhages at 4 weeks and jaundice recurred. Admitted at 5 weeks.

On examination (2.2.52).—Pale, jaundiced and ill. Firm, hemispherical encapsulated subcutaneous bruises, up to ½ in. in diameter over bony prominences. No petchiæ except a few on palate. Liver slightly enlarged: spleen impalpable.

Investigations.—Hb 62% falling rapidly to 45%. W.B.C. 20,000 rising to 54,000 (69% polys.). Coombs' test negative. Prothrombin not detected and blood would not clot. Serum bilirubin 6 mg. % (3·8 mg. direct). Alkaline phosphatase 27 K.A. units. Thymol and $ZnSO_4$ turbidity tests normal. Stool: positive occult blood reaction. Urine showed only transient bile pigment and a normal chromatogram. W.R. and Kahn negative on child and parents. Mother found to have serum alkaline phosphatase of 32 K.A. units one week after onset of Anne's illness.

Treatment and progress.—Vitamin K and protamine sulphate six-hourly. Jaundice increased; clotting time became normal in three days, but prothrombin time was still greatly prolonged and did not reach normal for another week.

On third hospital day brief convulsions occurred: these were mainly right-sided, but eyes would rove independently. Fontanelle bulging. Subdural taps negative and C.S.F. from left ventricle normal. For next three days, critically ill with occasional fits and developed right partial ophthalmoplegia. Liver enlarged rapidly and spleen slightly. Given transfusion of 400 ml. fresh blood followed by plasma and Hartmann's solution. Vitamin K continued, with penicillin and a course of crude liver extract. Recovery then rapid and within four weeks of onset the icterus had cleared and the hepatomegaly was subsiding.

Biopsies postponed till jaundice had cleared for fear of hæmorrhage. Skin nodule proved to be hæmatoma without any evidence of an infective process.

Liver biopsy (Dr. M. Bodian).—"The architecture of the liver parenchyma is normal. There is evidence of moderate bile retention in the form of plugs in bile canaliculi and in granular form in a minority of binucleated large liver cells which are especially aggregated in the centri-lobular areas but by no means conspicuously so. There is no evidence of bile duct proliferation nor do the portal bile ducts contain bile. Lymphocytic infiltration in the portal areas is minimal. There is sufficient evidence of hepatitis of a type which ought to regress without residual liver changes."

Later progress.—At 5 months, right cranial hemiatrophy with vacant look, spastic limbs and frequent myoclonus. Major fits occurred later. At 20 months left hip was dislocated: orthopædic attempts at reduction have failed, largely because of the myoclonus.

Present state (aged 2 years 11 months).—Head circumference 16¾ in. Right parietal bone depressed, particularly posteriorly. Right face smaller. Convergent squint. Can see and hear but pays very little attention. Nutritional state excellent. Liver and spleen normal. Mentality: extreme retardation.

C.N.S.—Cranial nerves probably normal. Fundi normal. Limbs are variably spastic, right leg worse than left. Frequent myoclonic jerks (worst in right leg); occasional brief grand mal seizures.

Discussion.—The most unusual features of this case are the extreme degree of the disturbance of blood clotting, the severity of the encephalopathy and the sequelæ of gross mental defect and epilepsy. It is possible that other mechanisms (e.g. heparin liberation) as well as prothrombin deficiency were responsible for the hæmorrhagic state, as the clotting time became normal so much more quickly than the prothrombin time. The pathogenesis of the cerebral catastrophe can only be surmised, but intracranial bleeding was excluded, and as the C.S.F. was normal it seems most probable that the distension of the fontanelle was due to extreme œdema of the brain. The asymmetrical microcephaly, gross mental retardation and varied epileptic seizures suggest widespread brain damage of considerable severity. Air encephalography would be of great interest but has not seemed justifiable.

The finding of a high serum alkaline phosphatase in the mother is unusual, as is the degree of leucocytosis in this case.

L. MAY

Hemihypertrophy Left Side of Body. Congenital Lymphatic Œdema of Left Arm. Radiological Enlargement of Heart Shadow.—TREVOR P. MANN, M.D.

K. H., aged 6½ years. Left arm large and œdematous from birth. During early months of life, left side of face, left buttock and thigh noted to be larger than right. Infantile eczema from age of 9 months; asthma since the age of 2 years.

Chest X-ray (December 1952) (Fig. 1).—Enlarged globular heart shadow suggestive of pericardial effusion. Generalized diminished translucency of left lung field compared with right. Left pleura thickened.

Examination (Fig. 2) showed asymmetry of face and anterior chest (left side more prominent than right); girth of thigh and calf greater on left side (left leg slightly longer than right); left arm grossly enlarged, heavy and œdematous. Thickening of the skin and subcutaneous tissues of left half of body. Slight œdema of left upper and anterior chest wall. Percussion note impaired over left clavicle and left anterior chest; cardiac and liver dullness noticeably diminished (asthmatic subject). Cardiovascular system normal. ECG normal.
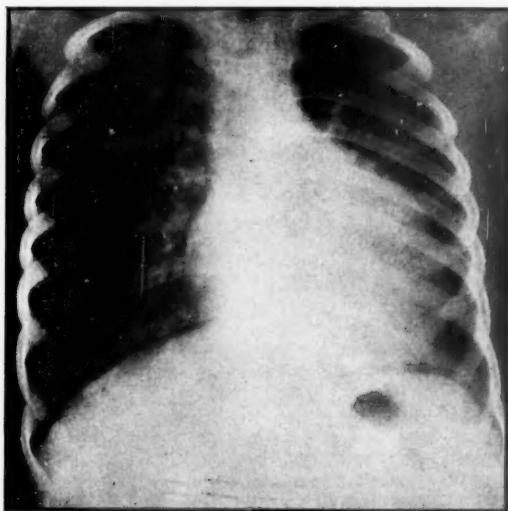

FIG. 1.—Enlarged globular heart shadow suggestive of pericardial effusion. Generalized diminished translucency of left lung field.

FIG. 2.—Photograph showing grossly enlarged, heavy and œdematous left arm and asymmetry of face, trunk and thighs.

Radioscopy of heart (January 1953).—"The cardiac movements are very shallow and hardly visible. This tends to confirm the diagnosis of pericardial effusion."

Recently the X-ray changes have been reviewed with the help of Dr. J. Rubin.

"The *appearance* of the heart shadow, both in films and on screening, remains unchanged. The diminished translucency of the left chest and the pleural thickening on the left side persist. X-ray of wrists shows that the bone age is the same on the two sides.

The points in favour of pericardial effusion at the first examination two years ago were: (1) The widened and rounded cardiac shadow. (2) The absence of obliteration of the right cardiophrenic angle. (3) The poor cardiac pulsation.

The points which are now against pericardial effusion are: (1) The absence of change of shape or size on comparison of serial films over a period of eighteen months. (2) The absence of alteration of shape with change of posture. (3) The absence of distension of the posterior inferior recess of the heart in the right lateral view.

The appearances are thus more in favour of cardiac enlargement due to some obscure cause. The possibility of greatly thickened or infiltrated pericardium or myocardium should be considered."

Conclusion.—The child appears to have a congenital lymphatic œdema of the left arm. Presumably the other changes on the left side of the body are due to an abnormality of the lymphatic tissues. It is possible that the X-ray changes are due to an intrathoracic lymphatic abnormality affecting the pleura and pericardium. No reference to this syndrome has been found in the literature.

Dr. N. E. France: A 4-year-old girl under the care of Dr. C. T. Potter suffered from a similar condition to this case. A biopsy at 2 months of age showed subcutaneous lymphangiectasia. At autopsy diffuse lymphangiectasia was also found to involve the intestine, mesentery and lungs, in the first producing a condition similar to Whipple's disease and in the lungs giving pleural thickening. The pericardium was unaffected but there was a large pericardial effusion.

Intrathoracic Enterogenous Cysts with Vertebral Malformations and Unilateral Paralysis of the Diaphragm.—W. MESTITZ, M.D.

C. N., male, aged 6 months. First child of a 39-year-old mother who has been married for thirteen years. The pregnancy was normal, but fœtal distress was the indication for forceps delivery. B.W. 6 lb. 9 oz. He was shocked at birth and required resuscitation. On the 5th day he had a cyanotic attack after a feed and had to be placed in oxygen. The respirations became rapid and laboured, with marked indrawing of the lower ribs. During the following twenty-four hours the condition deteriorated rapidly and he was transferred critically ill to the Royal Alexandra Children's Hospital, Brighton. On admission, he was cyanosed in spite of continuous oxygen, the respirations were gasping and intermittent. Next day he was much improved, the breathing more regular and deeper and the cyanosis less, so that an indwelling polythene tube could be passed. Dullness and diminished breath sounds were present over the right lower lobe.

FIG. 1.—Large dense homogeneous mass with a rounded lateral margin in the right middle and lower zones with translucent lung present in the right costophrenic region. Massive displacement of the heart and mediastinum to the left. Spina bifida with hemivertebræ of the mid-dorsal spine.

An X-ray (Fig. 1) showed a large homogeneous mass with a rounded lateral margin in the right middle and lower zones with translucent lung present in the right costophrenic region. There was massive displacement of the heart and mediastinum to the left. Some of the films suggested that the mass consisted of two rounded opacities. The baby was fairly well while in oxygen but when taken out became cyanosed with shallow, laboured and irregular respirations. Attempts to start bottle feeding at the age of 8 weeks produced cyanosis. Feeding by polythene tubing was continued and he continued to gain weight. His temperature was normal throughout.

Repeat X-rays revealed in the lateral views the mass with its sharply defined rounded margin lying behind and overlapping the heart. A.P. views also showed spina bifida with hemivertebræ of the mid-dorsal spine. On screening the most striking feature was paradoxical movement of the right half of the diaphragm. At the age of 2 months he passed some altered blood *per rectum* and this recurred four weeks later, when there was fresh blood as well.

In September his weight was 12 lb. and he was fit for thoracotomy (Mr. A. H. M. Siddons, Victoria Hospital, Tite Street). I am indebted to Mr. Siddons for the following report: A large mass, consisting of one large and one smaller cyst arising from the right paravertebral gutter was present, lateral and posterior to the œsophagus, and just below the azygos vein. It was not possible to define the structures from which the pedicle arose but there was no obvious connexion with the œsophagus. The larger cyst was aspirated and removed and the smaller dissected. Feeding by spoon could be started immediately and soon he learned to suck and could be put to the breast. After operation progress was uninterrupted, except for one further minor episode of melæna. He is now 7 months old and weighs 16 pounds.

The pathological report (Professor T. Crawford) says that the wall of the larger bilocular cyst resembles that of the stomach. The epithelium is fundal in type with mucus-secreting, zymogenic and oxyntic cells. There is a well-defined submucosal and muscle layer present. The epithelial lining of the smaller, unilocular cyst resembles that of the gastric cardia. Its wall is composed of smooth muscle.

Comment.—Enterogenous cysts of the mediastinum, first described by Wyss in 1870 are uncommon. The subject has been recently reviewed in detail by Fallon, Gordon and Lendrum (1954). They arrived at the conclusion that none of the various theories of their origin put forward so far is acceptable, chiefly because none takes into account the simultaneous occurrence of the vertebral anomalies. They regard the cysts as the final product of an incomplete separation of the notochord from the embryonic alimentary tract.

Apart from these vertebral anomalies, which are present in more than half the published cases, our case showed the following particular features:

Difficulty in swallowing: This is frequent and may lead to malnutrition. In our patient it was most marked, and feeding by indwelling polythene tubing proved invaluable. It is interesting to speculate whether the worsening of symptoms during and after feeds may have been due to an increase in the size of the cysts caused by reflex activity of the secreting glands.

Hæmoptysis and hæmatemesis are mentioned in the history of several cases, but only in 4 cases could I find a mention of melæna. Our patient had three attacks, two before and one twelve days after operation. We did not connect this symptom with the underlying condition until Mr. Siddons drew our attention to it. He assumed that a fine duct connected the intrathoracic cyst with some intra-abdominal part of the intestinal tract. Such connexion, although rare, can occur and the fact that it could not be found at operation does not exclude the presence of a very fine channel. However, the melæna recurred after operation and this seems to point to the presence of a similar abdominal cyst or duplication. This combination was found in nearly a third of all reported cases.

A striking feature of our case was the unilateral paralysis of the diaphragm: This has never been described before in association with intrathoracic enterogenous cysts, and although it affected the side of the cysts, it is open to discussion whether the two conditions were not coincident. Unilateral paralysis of the diaphragm in the newborn is known. It is usually associated with Erb's palsy but several cases of isolated paralysis of the diaphragm, more commonly on the right side than on the left, have been described.

Enterogenous cysts are always situated in the posterior mediastinum, with few exceptions on the right side, and should be considered in the differential diagnosis of unexplained shadows, with or without clinical symptoms. A most important diagnostic point is a coexistent vertebral anomaly. Aspiration of the contents for chemical examination and injection of radio-opaque substances have been recommended. This procedure, although technically easy, should not be attempted because of the possibility of leakage along the needle track with danger of digestion of lung.

The treatment is surgical—thoracotomy and one-stage excision if possible.

The reported case is one of the youngest operated on successfully.

My thanks are due to the radiologist, Dr. J. Rubin, for his invaluable help.

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Recurrent E. *coli* Meningitis and Persistent Cauda Equina Syndrome due to Congenital Dermal Sinus.—JOHN LORBER. M.D., M.R.C.P.

R. C., aged 3½ years. *History.*—Admitted to another hospital at 3 months of age with an acute purulent meningitis. A profuse growth of *E. coli* was obtained from the C.S.F. After treatment with penicillin and Sulphamezathine he recovered, but relapsed a few days later and he was again treated with penicillin with slow response. On each occasion acute diarrhœa preceded the symptoms and signs of meningitis.

He was readmitted to the same hospital when 13 months of age with a third attack of meningitis. *E. coli* were again isolated from the C.S.F. This organism was reported to be sensitive to Sulphatriad, streptomycin and chloramphenicol, and insensitive to penicillin and Aureomycin. There was no response to systemic penicillin and sulphonamide treatment, so later he was treated with intrathecal streptomycin as well, with some improvement.

He was transferred to the Children's Hospital, Sheffield, on July 22, 1952, then aged 14 months. On admission he presented the signs and symptoms of an acute meningitis (cell count in the C.S.F. was 640/c.mm. and the protein 500 mg. %); there was a small sinus in the lower lumbar region from which a tuft of hair protruded and which was surrounded by a nævus (Fig. 1); and he had a complete cauda equina compression syndrome—a large bladder with retention overflow, a weak anal sphincter and complete flaccid paralysis and anæsthesia of both feet. It was considered that the recurrent meningitis was due to infection ascending through a congenital dermal sinus to the meninges and that the lower end of the spinal cord was probably compressed by an infected intraspinal dermoid associated with the sinus.

The plan was to control the meningitis and then to attempt to excise the dermal sinus. A combination of parenteral streptomycin and sulphadiazine with intrathecal streptomycin was ineffective, so chloramphenicol was given for five days. There was no clinical improvement, the child developed convulsions and the C.S.F. became more purulent. In view of these events it was decided to try polymyxin B (obtained through the courtesy of Dr. H. J. Parish of the Wellcome Research Laboratories). It was given intramuscularly (100,000 units six-hourly) and intrathecally (25,000 units daily) in conjunction with oral sulphadiazine. The meningitis practically cleared after eight days of treatment and at this stage he was transferred to a Neurological Unit (Mr. J. Hardman). A myelogram demonstrated the


site of the stalk of the dermoid penetrating the spinal canal. A laminectomy was performed and the sinus was found to communicate with a dermoid cyst within the spinal canal which compressed the spinal cord and it was attached to the dura. The sinus track and the dermoid were removed. The cyst contained hair and cheesy material. A swab from the wall of the cyst yielded on culture a heavy growth of *E. coli* sensitive to 2·5 units/ml. of polymyxin. After operation intrathecal polymyxin treatment was continued for eight days and intramuscular polymyxin for two days. C.S.F. levels of between 10·1 and 2·5 units/ml. of poly-

FIG. 1.—Dermal sinus with tuft of hair, before operation.

myxin were found between ten and twenty-four hours after instillation.

On his return to the Pædiatric Unit he again had signs of a purulent meningitis, this time due to a *Staph. aureus*. The same organism was obtained from the unhealed wound on his back. It was only slightly sensitive to Aureomycin *in vitro* (50 µg./ml.), nevertheless he made a good and final recovery on Aureomycin treatment.

On discharge home he was very well and active, but his complete cauda equina syndrome persisted. In the next two years there has been no significant improvement in this respect and he can only walk with the aid of calipers. He is anæsthetic below his thighs and has developed painless ulcers on his toes and a painless effusion into his right knee-joint. He remains incontinent of urine and fæces. He is still subject to fits in spite of sedation.

Comment.—The association of congenital dermal sinuses with recurrent meningitis is well known. As even the first attack of meningitis may be fatal or lead to serious sequelæ, it is suggested that a congenital dermal sinus in the mid-line over the spine or on the cranium should be explored and removed, if discovered by routine examination. Such a sinus should always be looked for in cases of meningitis, especially if the meningitis is recurrent or is due to an unusual organism. The value of polymyxin in *E. coli* meningitis is worth bearing in mind if the infection does not respond to the other antibiotics and sulphonamides. Attention is drawn to the severe sequelæ from spinal compression from infected intraspinal dermoids.

Glycogen Disease Occurring in a Boy with Congenital Morbus Cordis (Patent Interventricular Septal Defect).—L. FIRMAN-EDWARDS, M.D., M.R.C.P.

This case combines a congenital with a metabolic defect in a boy whose father was of pure Mediterranean stock. Glycogen disease is reported as being extremely rare in Mediterranean races, yet the father was believed to have had a liver complaint in boyhood and had a large abdomen, while the mother and her family were all quite normal. Unfortunately he was killed in action during World War II, so I have been unable to confirm the above statement. He was a Corsican in the Free French Navy; the mother is English.

G., male, born 2.4.45. Birth-weight 4½ lb.

Had frequent epistaxes since age of 4. Found to have patent interventricular septum in April 1950. When seen by me at the local School Heart Clinic, was found to have a very large liver, smooth and not tender. Spleen not enlarged. The boy was very undersized—weight 31 lb. 2 oz., height 34 in. at age of 5½ years. He was admitted for investigation. Blood: Hb 55%, R.B.C. 3,220,000, W.B.C. 8.000 (polys. 44%, lymphos. 54%, monos. 2%).

Urine: acetone present, no glucose or albumin.   Glucose tolerance test: fasting blood sugar 44; half-hourly values 117, 103, 77, 45 mg.%.   Blood glycogen 2·1 mg.%.   Adrenalin sensitivity 45, 51, 54, 56 mg.%.   Urinary 17-ketosteroids 0·36 mg. per 24 hr.   Blood proteins, fibrinogen and prothrombin-time normal.   X-ray sella turcica normal.   Blood cholesterol 455 mg.%.

Treated with iron, vitamin K, high protein and carbohydrate, low fat diet, and injections of Antuitrin G, which was discontinued after some months owing to his violent objections.

9.10.51, Blood: Hb 82%.   R.B.C. 4,200,000; W.B.C. 5,700.   Glucose tolerance: 53, 100, 76, 95, 80 mg.%.

Present condition (aged 9 years).   His liver is a little smaller, but still well below costal margin.   His Hb is 88%.   Weight 43 lb.   Height 41 inches.   He has recently had extensive dental treatment for very carious teeth.   He is an undersized but very active and intelligent boy.

Comment.—I do not think there is any doubt about the diagnosis of von Gierke's disease in this case.   The chief peculiarities are its occurrence in the son of a man of Mediterranean stock and its apparent inheritance from that side of the family, and the presence of a septal defect in the heart independent of the glycogen storage defect and in the absence of mega-cardia, which has often been described in that disease.

Dr. C. Worster-Drought said that there was no doubt concerning the diagnosis in this case in view of the enlarged liver and the presence of acetone in the urine without glycosuria.   Provided the heart lesion remained at a satisfactory level, the ultimate prognosis should be good, as in most cases the liver becomes progressively smaller as the child grows and the acetonuria correspondingly diminishes.   In a case which he (Dr. Worster-Drought) originally showed before the Section in 1923 (*Proceedings*, **16**, Sect. Dis. Child. 56), when the child was aged 10, the girl had practically "outgrown" her disorder when she was shown again in 1935 (*Proceedings*, **28**, 829) at the age of 22; the liver was no longer enlarged and there were no symptoms except that she occasionally showed acetone in the breath and urine.   She was then 5 ft. 6 in. in height and weighed 9 st. 8 lb.   Now at the age of 42 she continues in good health, and no acetone has been detected in the urine on occasional examination for twelve years; she remains, however, somewhat intolerant of fats.

Familial Dwarfism associated with Microcephaly, Mental Retardation and Anæmia.—CLIVE UPJOHN, M.D. (for J. N. O'REILLY, D.M.).

These two children are members of a family who present this rare syndrome of dwarfism with microcephaly of unusual type and mental retardation.

The mother has been married twice.   By her first husband there is one son, who is now 23 years of age and is normal.   She has had 6 more children by her second marriage—the first 5 have all been dwarfs with the other features already mentioned—the sixth child is normal.   The first three born have all died of respiratory infections aged 7½ years, 9 months and 4¾ years.   The eldest was also grossly anæmic with hæmoglobin 22% at the time of his death.   There is no consanguinity between mother and father.   (*The two youngest dwarfs and the normal sibling, now aged 4 years, all attended at the meeting.*)

Case I.—T. W., male, aged 12.

Pneumonia aged 9.   Has suffered from recurrent respiratory infections and has bronchi-ectasis of middle and lower lobes of right lung.   During the past year has suffered from recurrent anæmia, the marrow showing pancytopenia, requiring repeated blood transfusions at intervals of a few months.   Pre-transfusion blood count: Hb 40%; R.B.C. 2,030,000; W.B.C. 3,000 (polys. 55%, lymphos. 44%) and platelets 85,000/c.mm.   Striking facial appearance, with superficially bright expression and behaviour; the latter is more like that of a child of half his age.   Marked disproportion in size of his cranium to his facial bones, the cranium being of small capacity.   Radiological bone age about 9 years.   Blood chem-istry normal.   Twenty-four-hour urinary 17-ketosteroids 0·1 mg./100 ml.   Height 47½ in. Weight 34½ lb.   Head circumference 16½ in.

Case II.—L. W., female, aged 9.

Strikingly similar facies to her brother, with relatively small skull.   No anæmia.   Has also had respiratory infections, but not so frequently as her brother.   No evidence of bronchiectasis.   Radiological bone age same as chronological bone age.

Blood chemistry normal.   Twenty-four-hour urinary 17-ketosteroids 0·4 mg./100 ml. Height 46 in.   Weight 31 lb.   Head circumference 16¾ in.

Both children have developmental defect of middle phalanx of both 5th fingers; also simian line on left palm.

The combination of microcephaly and anæmia and their association with pancytopenia of the bone marrow are features which are common to Fanconi's type of anæmia. It is possible that this diagnosis applies to these dwarfs but no skin pigmentation is present and the microcephaly is more marked than that usually associated with Fanconi's anæmia.

There are two previous reports of other families which bear a marked resemblance to

FIG. 1.—Shows the youngest and normal sibling aged 4 years on the left of the picture, next to him the two dwarfs who were shown at the meeting and a normal girl, 11 years old, who is included as a control.
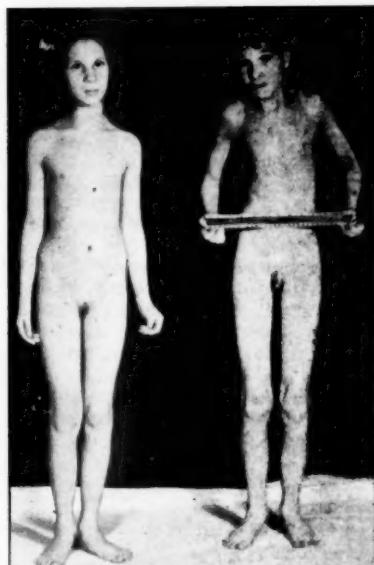
FIG. 2.—Shows the two dwarfs by themselves to demonstrate their configuration and facial appearance.

these dwarfs. In 1936 Cockayne reported a brother and sister who were two members of a family of 7 siblings, the other 5 being normal. Cockayne's cases show a marked similarity to the 2 children reported here. Cockayne wrote: "The dwarfs are so much alike in facial appearance, build and disposition that the same general description will suffice. Both have small heads; the vault of the skull is flattened and the circumference small. The general shape is normal and neither child has the receding forehead characteristic of microcephaly. Their faces are small with sunken eyes and prominent superior maxillæ. Their trunks are slender and their limbs long. Both children are active and their movements are quick and bird-like. They are friendly and playful, invariably good-tempered and laugh with obvious enjoyment at the slightest provocation. Although they are imitative, they have a certain amount of initiative. They are below the average intelligence and are far more excitable and laugh much more readily than children of normal mentality."

The second family previously reported was of 2 brothers, who were dwarfs, of a family of 4 siblings, the other 2 being normal. These dwarfs were shown to this Section by Neill and Dingwall in 1948. They had features similar to those reported by Cockayne but in addition they had a marked lordosis, tottering gait and intracranial calcifications.

There appear to be sufficient features common to the three families to justify grouping them into a clinical entity. This syndrome is probably due to a multiple germ plasma defect, the gene being recessive and, as Neill and Dingwall suggested, the condition may be allied to progeria.

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Agammaglobulinæmia.—DONOUGH O'BRIEN, M.D. (for B. BUCKLEY SHARP, M.D., M.R.C.P.).

J. G., aged 8 months, was delivered normally at full term, birth-weight 8 lb. 6 oz., and the immediate post-natal period was uneventful. Ten days after discharge from the maternity hospital the infant first attended the Out-patient Department with a purulent rhinitis. From then on he came to suffer alternately from upper respiratory infections with bronchitis, otitis media, purulent ophthalmia, coccal dermatitis and on one occasion gastro-enteritis. Altogether he attended Out-patients on 31 occasions and was admitted to hospital five times for a total of 55 days. With the aid of antibiotics he has recovered well from each infection, only to succumb again. In spite of this, he has thrived and remains on the 90 percentile for height and weight for his age.

Analysis of serum proteins showed that γ-globulin was absent or present in only minute amounts. There was also some increase in the α_2-globulin and the β-globulin migrated faster than normally.

For the last month he has had weekly injections of 250 mg. of globulin intramuscularly (*circa* 0·025 gram/kg. body-weight/week). Whilst this treatment appears to have restored his serum γ-globulin to approximately normal levels and the infant has continued to thrive he has still been subject to repeated upper respiratory tract infections.

Galactosæmia Presenting with Gangrene of the Right Foot.—L. HAAS, M.R.C.P., D.C.H. (for CHARLES NEWMAN, M.D., F.R.C.P.).

Gary H., aged 11 weeks. *History.*—Born at full term by normal delivery. Birth-weight 8 lb. Developed area of discoloration on the right heel on the 3rd day of life. This progressed to gangrene within twenty-four hours.

On examination.—Black, dry, gangrenous area involving sole and lateral side of right foot (Fig. 1). Liver edge palpable 2 fingerbreadths below costal margin. Tip of spleen felt. Prominent veins on abdominal wall. Bilateral cataracts (noted three weeks after admission).

Investigations.—Urine brick-red to Benedict's solution. Reducing substance identified as galactose during third week in hospital. No excessive amino-aciduria. Blood galactose 220 mg.%. Liver function tests normal. Serum electrolytes normal.

Progress.—Was given a galactose-free artificial milk mixture, and after forty-eight hours the reducing substance had disappeared from the urine. The area of gangrene healed slowly within the course of six weeks, with separation of black slough and granulation from below. Over the course of the next two months the liver gradually receded in size to being palpable only one fingerbreadth below the costal margin. The spleen could no longer be felt and the cataracts resolved. He was first noticed to smile at about the age of 10 weeks, and seemed to behave normally for an infant of his age. A hypochromic anæmia which developed during the first few weeks was corrected by a blood transfusion.

FIG. 1.—Showing an area of gangrene involving the sole of the right foot.

[Print taken from colour transparency and therefore reversed.]

Comment.—The most disturbing feature of galactosæmia is the high incidence of mental deficiency in the survivors. To forestall this complication, Komrower and Holzel (1954) believe it to be imperative to remove even small traces of galactose from the diet of the very young infants suffering from the disease. They recommend a mixture of egg, sugar and Farex with added calcium as a suitable diet (Holzel, 1954; Komrower, 1954) and this feed has been given to the patient described.

The ætiology of neonatal gangrene is obscure. Gross (1945) states that it is sometimes caused by an embolus carried into the systemic circulation from the ductus arteriosus, as the closure of this vessel may be accompanied by thrombosis of its entire lumen. It is of interest that Lawrence and McCance (1931) have reported a case of a 15-day old infant with areas of gangrene on a foot, wrist and both buttocks, who also had glycosuria and a raised blood sugar. As this child, however, made a complete recovery it is unlikely that he was suffering from galactosæmia.

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Section of General Practice

President—R. J. MINNITT, M.D., F.F.A. R.C.S., F.R.C.O.G.

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DISCUSSION ON THE PREMENSTRUAL SYNDROME

Dr. Raymond Greene:

Many years ago I introduced the term "premenstrual syndrome" to describe the numerous symptoms which occur in so many women during the week before menstruation; disappearing as soon as the menstrual flow begins. It seemed a more appropriate term than "premenstrual tension", because tension, though very common, is only a small part of the trouble. However, when, with Dr. Dalton, I began a more intensive study of the subject (Greene and Dalton, 1953) it became clear that the term is not a good one. The symptoms occasionally occur at mid-cycle, when they are presumably associated with ovulation; or they may appear during menstruation, or even, rarely, after it.

The symptoms are of extraordinary diversity, and are relevant to every specialty. The most important symptoms are *neurological*. In our first series of 87 patients we had 5 cases of epilepsy, 10 of migraine, and 26 of severe headache. Vertigo occurred in one. Outside the published series, we have seen several more patients with premenstrual *petit mal*. That migraine in women is commonly premenstrual has been stressed by Campbell (1951), by de Wit (1950) and by our ex-President, Sir Francis Walshe, in his textbook (1952). *Psychiatric* manifestations have been recognized for many years, especially that state of intolerable nervous tension or blackest depression which has broken up so many homes. During the final week of the cycle many women experience great or small degrees of irritability which they may fail to control; depression which may lead to suicide; lethargy which may make it almost impossible for them to continue their work. Women air pilots may lose their skill and unaccountably crash (Whitehead, 1934). French figures show that 84% of crimes of violence by women are committed during or immediately before the menses (Cooke, 1945). In another series (Morton *et al.*, 1953) it was found that crimes of violence had been committed in 62% of cases in the premenstrual week, in 19% at ovulation time, in 17% during menstruation, and in only 2% in the week after menstruation. I am at present investigating this subject in collaboration with Dr. T. Christie, of Holloway Prison. I am also beginning an investigation into the cyclical changes of mood which occur in psychotic patients. The phases of the moon have been known since the most ancient times to influence their behaviour. How many of us, using the word "lunatic", have suspected that we were referring to the premenstrual syndrome?

In dermatology, a cyclical variation in symptoms is often to be observed. We saw, among our 87 patients, 2 with acne of the face, and 2 with acne of the shoulders and back, 1 with styes, 1 with seborrhœic dermatitis, 1 with eczema, and 1 with erythema multiforme, all occurring during the premenstrual phase and at no other time. Still commoner are premenstrual exacerbations of skin lesions present throughout the whole cycle. Dentists often observe cyclical changes in the oral mucous membranes at this time. In our series there were 2 with severe ulcers of the tongue. I am at present collecting further observations about this in collaboration with Mr. Norman Ainsworth. In the field of the ear, nose and throat, surgeons have been interested for at least seventy years in the hyperæmia and œdema of the nasal mucosa which occur premenstrually and which may cause the regular monthly occurrence of sinusitis, vacuum headaches and rhinorrhœa. Respiratory disorder is represented too, for in our series there were 4 patients with cyclical asthma. Orthopædics is represented by premenstrual backache, perhaps due to the hygroscopic properties of the nuclei pulposi (Naylor and Smare, 1953) and by a variety of aches and pains in joints and soft tissues which may well be due to hydropsy of fat (Copeman, 1949). In the field of ophthalmic surgery, one case of premenstrual glaucoma has been described (Lagrange, 1925)—a subject to which Dr. Dalton has recently given some attention. Finally, when studying our published series, we were impressed by two findings which can hardly fail to interest the obstetrician, the resemblance between the symptoms of our syndrome and those of toxæmia of pregnancy and the frequency with which the two conditions occurred in the same patients (Dalton, 1954).

There is one common factor in all these widely differing disorders. In almost all cases there is a sudden gain in weight from 2 to 14 lb., associated in severe cases with oliguria,

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pitting œdema and bloating of the abdomen, all relieved by a diuresis at the beginning of the menstrual flow.

A shift in the œstrogen-progesterone ratio may be responsible for this retention of water (Greene and Dalton, 1953), as witness the periodicity of the symptoms—for œstradiol and progesterone are the only hormones proven to fluctuate regularly throughout the normal menstrual cycle. Again, there is the complete relief of symptoms during pregnancy, when the secretion of progesterone is so high. We were early struck by the exceptions to this rule, the toxæmic women whose symptoms were accentuated or who then came to suffer from them for the first time. Toxæmia of pregnancy and habitual abortion have long been suspected as being due to progesterone deficiency, but suspicions were dulled by the results of uncritical clinical experiment; doses of progesterone we would now regard as homœopathic were administered in vain. An experiment is now under way with Dr. Sara Field-Richards in the Philip Hill Clinic at the Royal Northern Hospital in which "heroic" doses of progesterone are being used in an attempt to prevent miscarriages.

To me it appears that this hypothesis is too facile. Few disorders in endocrinology are so simply explained. On this hypothesis alone it is difficult to explain the occasional cases of cyclical but aberrant attacks, and the premenstrual hypoglycæmia observed by Morton and others (Morton, *et al.*, 1953; Billig and Spaulding, 1947). We must remember that the ovarian tides are not the only ones the moon appears to control. The adrenal cortex has also its ebb and flow, and it is tempting to follow Geiringer (1951) and to attempt in some cases to incriminate these glands as well. Dr. MacKinnon (1954), working in part on my patients, has been able to show that fewer sweat glands are active during the premenstrual phase, and she suggests that this change may be attributable to alterations in adrenal activity. She cites reasons for suggesting that there is an increased secretion of adrenal cortical hormones in the premenstrual phase in preparation for pregnancy, initiated perhaps by a change in pituitary hormone activity. Landau (1954) has reported that progesterone produces general protein catabolism and salt diuresis, antagonized by adrenal hormones, an effect most distinct in partial adrenal deficiency. These observations must arouse the suspicion that some form of adrenal over-activity may play a part in our syndrome. On the other hand Geiringer has pointed out that the singular susceptibility of some women to allergic phenomena in the premenstrual phase points rather to a withdrawal of steroid protection from hypersensitive shock organs. One cannot but agree with him that no conclusions on pathogenicity can be drawn from our undoubted proof of the relief of symptoms by the use of the pharmacological action of progesterone.

In the work now in progress on this subject in my laboratory, the suggestions brought to my notice by Dr. John Sophian cannot be neglected. He has suggested that excess of œstrogen might cause the breakdown of adenomyosine into adenylic acid, which, as Homer Smith has shown, reduces the glomerular filtration rate in the kidneys. This reaction occurs in the myometrium, and it was therefore interesting to observe whether the premenstrual syndrome could occur in women after hysterectomy. We have found that it does. Not only does hysterectomy fail to cure the premenstrual syndrome, but it may actually initiate it, a fact which we have so far failed to explain.

Before we can solve these problems, we must await the evolution of more practical methods for the evaluation of the various adrenal and ovarian hormones in blood and urine. Meanwhile, we want to relieve our patients. Some can be relieved by the orthodox methods of dehydration, the limitation of salt and water and the administration of diuretics, of which urea in full doses is still the best. Those who remain waterlogged despite these measures can still be relieved by progesterone. I will leave it to my collaborator, Dr. Dalton, to deal with the practical details of treatment.

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Dr. Katharina Dalton:

Three brief case histories will best illustrate the diverse presentations of the premenstrual syndrome.

Case I.—A mother of two young children put her head in a gas oven. On discharge from the mental observation ward she was reported as being "rational and genuinely sorry for her action, which followed a family quarrel". Three weeks later she was seen again. She was weeping, acutely depressed and anxious to take her life. Her husband readily confirmed that while she was normally happy and energetic, she always became depressed and irritable when her period was imminent, "she suddenly changes, she looks for quarrels, I can't do anything to please her". She was treated with 50 mg. progesterone and 2 c.c. mersalyl, and some sodium amytal to ensure a good night's sleep. The following day menstruation commenced and she was laughing again. She has since remained on progesterone and there have been no further attacks of acute depression.

Case II.—A housewife of 34 years was first seen in the early hours of the morning in an acute asthmatic attack. The severity of the attack warranted the use of adrenaline. Later that day a full history revealed that these acute attacks of asthma occurred every month, always on the first day of menstruation, and that her only periods of freedom from asthma had been during her three pregnancies, when she had felt remarkably fit. Asthma had first occurred at the age of 17 years coinciding with her first menstruation. She responded excellently to 10 mg. progesterone daily, and in December 1948 Dr. Raymond Greene gave her a 500 mg. progesterone implant. She has since remained in excellent health and had her fourth child in 1952.

Case III.—A married factory worker, aged 49, who had suffered from premenstrual migraine for years, developed ulcerative stomatitis in 1952. Observations over three months showed that the lesions commenced with a salty taste in her mouth on the 14th day of her menstrual cycle, and the following day moist, white and very painful ulcers developed on her lower lip and buccal mucous membrane. These persisted throughout the premenstruum, when her misery was increased by the addition of headaches, backache and depression; but all symptoms disappeared during menstruation. To use her words "progesterone acted like magic" on all her symptoms, and progesterone was later implanted.

The common factor in three apparently different cases was the recurrence of symptoms always at the same time in each menstrual cycle. To appreciate why such a variety of symptoms should all respond to the same hormone, progesterone, let us assume that Banting's and Best's momentous discovery of insulin had preceded Fehling's and Benedict's test for the detection of glycosuria. Banting and Best would have found that insulin could cause a miraculous response in some cases of coma, a dramatic recovery in some cases of emaciation, perpetual fatigue and polyuria, and a marked improvement in some cases of carbuncles and peripheral neuritis. It was the use of Fehling's and Benedict's test that enabled them to find a common factor in all these differing symptoms—the presence of glycosuria. In premenstrual syndrome there is a common factor—the cyclical recurrence of symptoms with each menstrual cycle. Unfortunately, there is no test to assist the diagnosis of premenstrual syndrome, or indeed of progesterone deficiency. To-day the recognition of this syndrome must depend on the intelligence of the patient, or her doctor.

DIAGNOSIS OF PREMENSTRUAL SYNDROME

The only positive diagnosis of premenstrual syndrome can be made by recording on a calendar the relationship of symptoms to menstruation. This point was illustrated in the case of a girl of 16 years, who had acute asthmatic attacks, always occurring on Mondays, not every Monday and not near menstruation. A three-month calendar, however, revealed a regular cycle of 28 days always commencing on a Tuesday, and an asthmatic attack always on the 13th day, a Monday, at ovulation.

Keeping a calendar necessitates delay in commencement of treatment, but there are certain factors which may assist the diagnosis of premenstrual syndrome. It is usual to find the presenting symptoms accompanied by bouts of depression, irritability and lethargy. Hippocrates ascribed these accompanying symptoms to "agitated blood seeking a channel of escape from the womb" (Bickers and Woods, 1951). One may suspect a patient who has boundless energy one day followed by a few days of lethargy and listlessness. Coupled with this is a tendency to blame a very minor symptom, such as a stye, ulcer in the mouth or acne, for the accompanying depression and lethargy, the impression being that if only this one little spot would disappear the mental tension would also follow suit.

Another guide is facial pallor and puffiness during an attack, suggestive at first sight perhaps of anæmia, but belied by the good colour of the mucous membrane and normal hæmoglobin level.

Spontaneous bruising has been noticed by Billig and Spaulding (1947) and others. It is painless, bilateral and usually in more or less the same area, with common sites on the thighs and upper arms. Possibly retinal hæmorrhages may be included here.

Signs, which may be noticed on day-to-day observations, are weight gain, œdema, albuminuria and hypertension. A weight gain and loss of over 2 lb. in a cycle is significant, although

Novak and Novak (1952) record the highest weight gain during the premenstruum of 15 lb. all of which was lost during menstruation.

Fig. 1 shows observations on a 40-year-old housewife with no children, who was suffering

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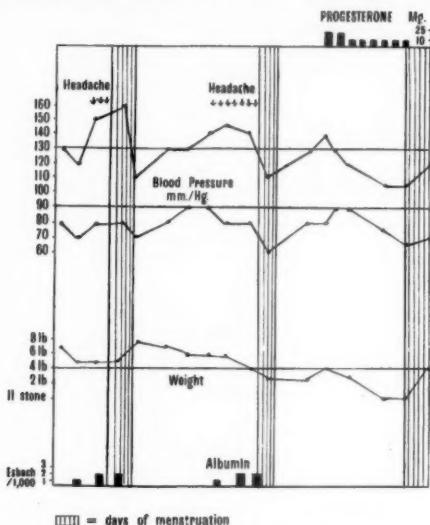
FIG. 1.—Blood pressure, weight and albumin in premenstrual syndrome.

from premenstrual headaches, depression and irritability. There was a rise in blood pressure from 110/70 mm.Hg after menstruation to 140–160/80 mm.Hg in the premenstruum, and the albuminuria, in catheter specimens, was limited to the premenstruum. Treatment with 25 mg. progesterone on alternate days produced uterine cramps (a sign of overdosage) but on 10 mg. progesterone there was relief on all symptoms, the blood pressure remained steady and there was no albuminuria.

Fig. 2 shows observations on a 42-year-old housewife, with no children, who was suffering
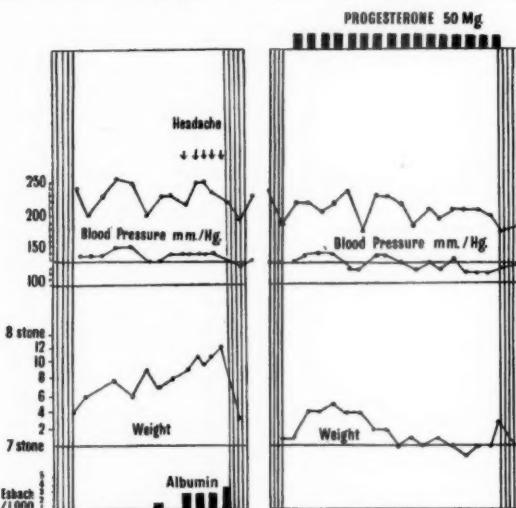

FIG. 2.—Blood pressure, weight and albumin in premenstrual syndrome with essential hypertension.

from premenstrual headache, depression, œdema and dyspnœa. It shows a weight gain of 11 lb. in a 7 st. woman, this weight being lost by diuresis during menstruation. Albumin was present in the premenstruum and there was an increase in ankle circumference from 7½ to 9¾ in. (these were early morning measurements). At the height of the œdema moist sounds were present in both bases of the lungs, accounting no doubt for the dyspnœa. The blood pressure was markedly raised throughout the cycle at a level of 200–250/120–130 mm.Hg. On treatment with 50 mg. progesterone alternate days she became symptom free, her weight and ankle circumference remained steady and there was no albuminuria. Nevertheless the raised blood pressure persisted at its previous high level throughout the cycle.
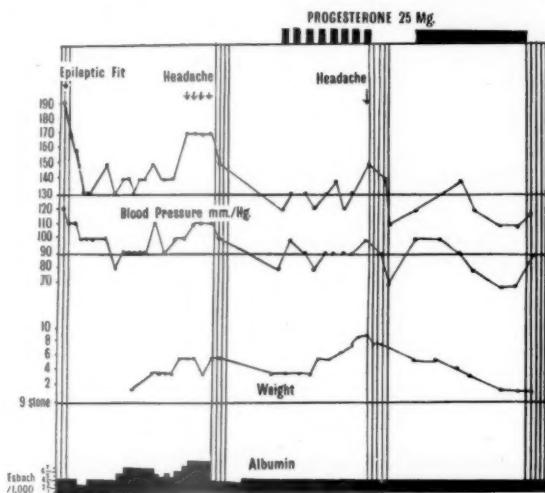

FIG. 3.—Blood pressure, weight and albumin in premenstrual syndrome with chronic nephritis.

Fig. 3 shows observations on a 40-year-old club hostess, who had been unemployed for six months owing to premenstrual epileptic fits and migraine. She was a widow, whose only pregnancy had been terminated at 28 weeks for chronic nephritis. Immediately prior to an epileptic fit she had a blood pressure of 190/110 mm.Hg, which dropped to 120 – 130 / 80 – 110 mm.Hg after menstruation. Her weight rose by 2 lb. and ankle circumference from 7½ to 8½ in. The albuminuria was present throughout the cycle. When treated with 25 mg. progesterone daily she became symptom free, blood pressure, weight and ankle circumference became steady, but the albuminuria persisted throughout the cycle. No epileptic

fits have occurred since commencing progesterone in September 1953 and she is now working happily as a shop assistant.

Obstetricians may recall that the same triad of signs (œdema, hypertension, and albuminuria) is present in another disease, toxæmia of pregnancy, and may also notice the resemblance of the three classes of toxæmia to these charts of premenstrual syndrome (Figs. 1, 2 and 3). There are those who, after a normal early pregnancy, develop œdema, hypertension, and albuminuria, just as in Fig. 1, after normality early in the cycle, these same signs of œdema, hypertension and albuminuria developed in the premenstruum. Those who show hypertension early in pregnancy, but later develop the superadded signs of œdema and albuminuria, are analogous to Fig. 2. Lastly, there is the class, which is analogous to Fig. 3, where albuminuria is present early in pregnancy with a later development of hypertension and œdema. These three charts also demonstrate the specificity of progesterone in acting only on those signs and symptoms present in the premenstruum, but not on signs and symptoms present throughout the cycle.

INVESTIGATION INTO INCIDENCE OF PREMENSTRUAL SYNDROME

This similarity of signs of œdema, hypertension and albuminuria, coupled with the high incidence of toxæmia noted in our reported series of premenstrual syndrome (Greene and Dalton, 1953) led to an investigation into the incidence of premenstrual syndrome in normal women and those who had previously suffered from toxæmia of pregnancy. A total of 952 women of child-bearing ages were interviewed. 614 were workers at a light engineering factory employing some 2,000 women workers, 101 were women attending routine sessions of an infant welfare clinic, and 237 were women who had previously suffered from toxæmia of pregnancy. 40 of these toxæmic mothers were from my partnership practice and 197 were selected from the records of the local antenatal clinics. The criterion for toxæmia was a blood pressure exceeding 140/90 mm.Hg and the institution of treatment (hospital admission, surgical induction or complete bed rest). 127 women were excluded for amenorrhœa, uncertain diagnosis or complicating factors, e.g. pyelitis, placenta prævia. These

figures satisfied the statisticians as there remained four almost equal groups, there were 191 toxæmic mothers, 222 parous controls, 176 non-parous married controls and 236 non-parous single women.

Diagnosis of premenstrual syndrome was made if there were attacks of any symptoms, which fulfilled the following three conditions: (1) they had been noted in each of the three previous menstrual cycles, (2) their severity demanded relief with analgesics or medical advice, (3) their occurrence at a specific phase of the menstrual cycle was confirmed by calendar. All women were interviewed by me and asked if they ever suffered from headaches, giddiness, nausea or vomiting, blackouts, asthma, backache, ulcers in the mouth, or any other symptoms they might care to mention, and were asked the day on which they last experienced an attack and if these had occurred more than three times in the last three months. Questions were asked on their well-being during pregnancy, past health, family health, their menstrual history and the day of their last menstrual period. They were given a form to complete, on which I wrote the recurring symptom and asked them to fill in the dates of the symptoms and of menstruation during the following six weeks.

Bickers and Woods (1951) noted the presence of premenstrual syndrome in 36% of women employees in an American factory of 1,500 women workers, Israel (1938) estimated that 40% of otherwise healthy women suffered from this syndrome, but Novak and Novak (1952), in their textbook, describe it as a "relatively rare but distressing disease".

My investigation showed an incidence of premenstrual syndrome of 30% in parous controls, 30% in non-parous married controls and 21% in single controls but that the high figure of 86% was recorded in toxæmic mothers (*see* Fig. 1, Dalton, 1954). The incidence of premenstrual syndrome obtained by calendar confirmation is very similar, and again shows a very high incidence among toxæmic mothers. Among controls, the effect of age was a gradual increase in the incidence of premenstrual syndrome, which was not present in the toxæmic mothers but which is not statistically significant (Fig. 4). The effect of parity on
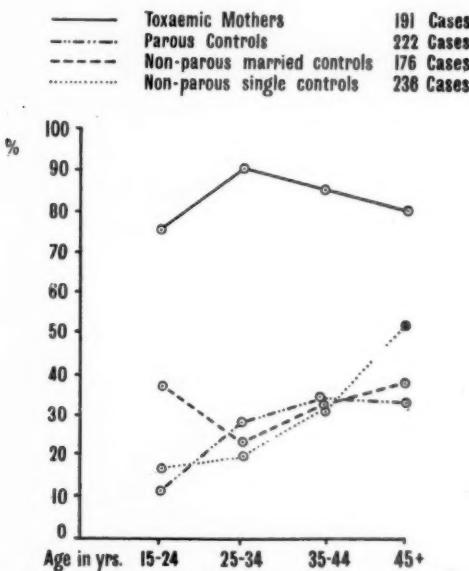
FIG. 4.—Effect of age on incidence of premenstrual syndrome.

the incidence was a steady and marked increase in toxæmic mothers (*see* Fig. 2, Dalton, 1954). These investigations confirmed our findings in premenstrual syndrome of a normal menstrual history in regard to duration of flow, length of cycle, age at first menstruation and absence of dysmenorrhœa (Greene and Dalton, 1953). Dysmenorrhœa was defined as pain coinciding with menstruation and present in the areas covered by uterine or ovarian nerve distribution, i.e. the lower abdomen and upper thighs. One often hears sufferers from premenstrual syndrome exclaim "Oh! my periods are quite normal, I never know I have them" implying

that because the menstrual flow is painless menstruation cannot be associated with the recurrence of migraine, asthma, depression or any other symptom.

The investigations also revealed that symptoms occurring during a toxæmic pregnancy tended later to recur during the premenstruum. Thus one mother who was troubled with nausea and vomiting throughout pregnancy would later find it was just these symptoms which recurred during the premenstruum. Another might develop headaches during the toxæmic pregnancy and later during the premenstruum, and yet another develop backache at both times. It was also noticed during the investigations, and since confirmed on toxæmic patients, that such symptoms antedated the onset of toxæmic signs by several weeks. This work suggested that both toxæmia of pregnancy and premenstrual syndrome have three stages of development. The first a stage of minor symptoms (headache, nausea, lethargy, depression, irritability, vertigo and visual aura, &c.), followed by a stage of signs (œdema, hypertension and albuminuria), and finally both diseases may culminate in fits, (eclamptic or epileptic).

The symptoms found by toxæmic mothers during their pregnancy and in the premenstruum, compared with symptoms noted in controls and in sufferers from premenstrual syndrome (Greene and Dalton, 1953), are shown in Fig. 5. Headache was the commonest symptom
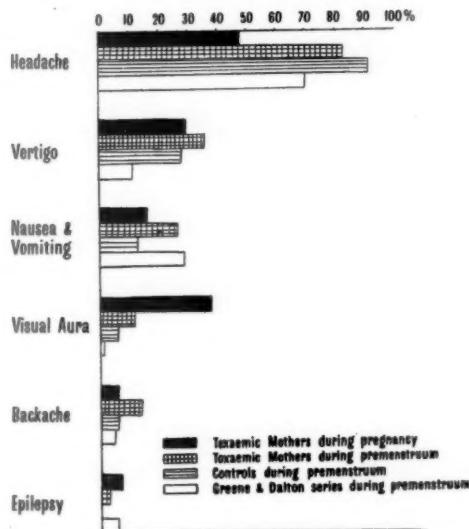
FIG. 5.—Symptoms during toxæmic pregnancy and in premenstruum.

in all classes. No specific questions were asked on lassitude, depression and irritability but these symptoms were frequently mentioned spontaneously. The absence of epilepsy in controls is accounted for by reason that epileptics are not eligible for employment at the light engineering factory at which most controls were employed.

THE COURSE OF PREMENSTRUAL SYNDROME

What is the course of premenstrual syndrome? In common with so many endocrinal disorders the onset is often associated with puberty, childbirth (normal or toxæmic) and menopause, but there may be a previous history of cyclical vomiting in childhood. In the investigation 26% of toxæmic mothers dated the onset of premenstrual syndrome before the toxæmic pregnancy, and only 34% dated the onset from the toxæmic pregnancy. There is a tendency for the symptoms gradually to increase in severity, but here stress undoubtedly plays an important part. At times of stress symptoms become unbearable and of increased severity, whilst when life flows along like a song the symptoms decrease or may pass by unnoticed. This makes it difficult to pinpoint the date of onset. Some patients were asked at each visit when the symptoms first commenced, but different answers were received on each

occasion. Thus one woman of 34 years, who was attending for premenstrual migraine, first mentioned symptoms of six months' duration; later this was extended to two years dating from her second toxæmic pregnancy; on another occasion marriage at 21 years was blamed; and yet another time she stated it had been present all her life, since her early school career. Undoubtedly headaches had been present since puberty and were antedated by cyclical vomiting, but they became severe at times of stress and it was on these occasions that treatment and hospital investigations were sought. Her daughter of 11, who has suffered from cyclical vomiting experienced her first true migraine the other day; she has not yet started menstruation. Her grandmother was also subject to premenstrual migraine, which ceased at the menopause.

Over the years the pattern of attacks may alter or symptoms change, as in Case III where ulcerative stomatitis gradually replaced migraine. Others have been seen where allergic rhinitis replaced asthma, or where migraine replaced, or was replaced by, epilepsy.

In our series of premenstrual syndrome we found a high incidence of toxæmia of pregnancy, but it is important to remember that we also reported that 62% were more energetic and free from symptoms during pregnancy (Greene and Dalton, 1953). In these cases it is probable that the extra progesterone produced by the placenta is responsible for the temporary remission. Indeed, those patients who are symptom-free during pregnancy, will sometimes return after a course of progesterone saying "I feel wonderful—just as if I'm pregnant".

Most cases end with the natural menopause, but not all, and in particular I would mention the increase of symptoms so common at times of the first missed periods. Others continue with monthly attacks during their sixth and seventh decades. I have at present under my care a woman of 52 years, who had a natural menopause eleven years ago, and who brought me a calendar covering the last twelve months showing a regularly recurring monthly attack of migraine. Another, aged 64 years, had monthly attacks of blackouts and vertigo, now relieved by ethisterone, and another aged 70 years, had regular attacks of asthma, also relieved by ethisterone. But my best example is a woman aged 63 years, who developed eclampsia with her fifth pregnancy twenty-six years ago. She had since suffered from attacks of epileptic fits every month, and after a natural menopause at 52 years, these attacks occurred every fortnight. In September 1953, after epilepsy of twenty-six years' duration she was treated with ethisterone 150 mg. daily and has since had no fit.

Hysterectomy certainly does not cure premenstrual syndrome, although it does transfer the patient from the gynæcologist's wing to a specialty dictated by the site of the symptoms. When you recall the loss of 11 lb. weight during menstruation by the woman shown in Fig. 2, realizing that this was water lost by diuresis in a couple of days, you may realize how it is that sometimes we are shown a pail of blood-stained urine which the patient is reputed to have passed in an hour or two and are told that her "Life's blood is coming away". This patient is regarded as having heavy periods, functional menorrhagia, and possibly as being a suitable case for hysterectomy. We, general practitioners, who have the later care of these patients, know that while hysterectomy may sometimes relieve the initial stress, such patients later return to our care with numerous symptoms for which no adequate cause can be found. They are labelled "neurotic", but perhaps it would be kinder to mark them as having a lowered threshold of pain. Fortunately, even these patients, if there is a cyclical recurrence of symptoms, respond readily to progesterone or ethisterone. At present I have under my care 13 cases of post-hysterectomy premenstrual syndrome, all of whom have responded to treatment.

It is too early to decide yet whether remissions following a course of progesterone or a progesterone implant are permanent. Certainly remissions do occur, as in the woman with severe premenstrual asthma in my opening case who has now had a remission of almost six years, but more often periodic treatment is needed. These patients are best classed as potential sufferers, in whom at times of stress there is likely to be a recurrence.

PROGESTERONE THERAPY OF PREMENSTRUAL SYNDROME

Although other treatments of premenstrual syndrome have been tried I always return to progesterone for consistently good results, and this alone will be discussed.

The results obtained in 78 cases of premenstrual syndrome treated by Dr. Raymond Greene and myself (1953) between 1948 and June 1952 when using progesterone or ethisterone are shown in Table I. 47·9% cases had complete relief following ethisterone and a further 17·4% improved. In the light of present knowledge it seems probable that this figure of "17·4% improved" could have been converted to "symptom free" if increased dosage had been used. Progesterone gave complete relief in 83·5% and improvement in 6·6%, but again with increased dosage this "6·6%" might have become symptom free.

Result	Ethisterone		Progesterone		Total	
	No.	%	No.	%	No.	%
Symptom-free	22	47·9	51	83·5	66	84·7
Improved	8	17·4	4	6·6	6	7·7
Postponed attack	1	2·1	—	—	—	—
No relief	14	30·5	4	6·6	3	3·8
Not known	1	2·1	2	3·3	3	3·8
Total	46	100·0	61	100·0	78	100·0

Ethisterone, or anhydro-oxy-progesterone, is an oral preparation of progesterone, which has been found also to have œstrogenic and androgenic properties (Emmens and Parkes, 1939). In treatment ethisterone was not effective in 30·5% cases, which may be due to lack of absorption or to its other properties. I have seen a few cases where ethisterone caused nausea and vertigo, symptoms which were not present when progesterone was used. Nevertheless the ease of oral administration makes it the drug of choice in mild cases of premenstrual syndrome and in post-menopausal women. The usual starting dose is 30–75 mg. daily which may be increased, even up to 250 mg. if there is no improvement and no side-effects. If side-effects are present these may disappear with lower dosage, or with progesterone.

Progesterone must be administered by deep intramuscular injections and can be obtained in oily or aqueous suspension. Results in Table I were obtained with the oily preparation. Progesterone must be given daily or on alternate days. Larger individual doses, instead of giving a longer duration, produce signs of overdosage. Signs of overdosage are euphoria, insomnia, restless energy, dysmenorrhœa (which in toxæmia may resemble false labour pains), faintness and possibly hysteria. There may be ovulatory bleeding or a slight blood loss throughout the premenstruum. Severe overdosage, such as may follow an implant, can cause temporary faintness, sudden lowering of the blood pressure and muscular weakness of a myasthenic type. Progesterone may also delay the onset of menstruation (and there is some evidence that it may delay the onset of labour). Occasionally urticarial weals and deep muscular tenderness follow an injection. I usually commence with 25 mg. alternate days, but if this does not give complete relief the dose is given daily, and if necessary larger dosage is used. The usual course is from the 14th to 26th day, but if ovulatory symptoms are present, if signs of weight gain are present before the 14th day or if a postponed attack of symptoms occurs during or after menstruation then the injections are continued throughout the cycle.

Where water retention is present to a marked degree less progesterone will be required if daily urea or ammonium chloride is used or if mersalyl is given twice or thrice weekly (mersalyl can be given in the same syringe as progesterone). While this makes for less expensive treatment, dehydration alone rarely brings that complete relief of all symptoms and that sense of well being which is such a feature of progesterone therapy.

Although progesterone is ideally commenced before the onset of symptoms, one is sometimes called in during an acute attack of asthma, migraine, psychosis, epilepsy, or of depression as in Case I. These attacks can often be cut short by the simultaneous injection of 50–100 mg. progesterone and mersalyl 2 c.c. This may be of academic interest only in some symptoms which respond equally well to other methods, e.g. adrenaline in asthma, but some acute cases of migraine, psychosis and depression can be relieved in four to five hours with this double injection.

To obviate the necessity of frequent injections a progesterone implant may be given, after complete relief of symptoms has been obtained with progesterone injections. I usually follow Dr. Raymond Greene's method of implanting 500–800 mg. progesterone in the abdominal fat through a 1/4 in. incision using local anæsthesia. Unfortunately progesterone pellets are very liable to be extruded although why this should occur is at present unknown; strangely enough extrusions rarely occur during pregnancy. I have seen extrusions occur within two weeks and others as late as sixteen months after insertion. It is interesting that the site of the pellets often becomes red and tender during menstruation, and more rarely at ovulation, and then the site may settle down only to reappear with the next menstruation. There may be fluctuation or discharge of a sterile fluid at the site of the implant during menstruation for a month or two before the extrusion of a pellet. The pellet is usually extruded through a punched-out hole, which heals rapidly within a day or two.

The other difficulty with progesterone implants is the uncertain duration of effectiveness, which does not depend on the type or the severity of symptoms or on the patient. Indeed

two implants on the same patient may have different durations. We have carefully che ked the batch numbers of pellets, but there is no correlation. It is possible that the amou t of stress received plays a part in determining the duration, but this is yet another proble: we are seeking to answer. The best time to implant progesterone seems to be at the e: d of menstruation and after any deficiency has been corrected by a course of progesterone.

There are conditions amenable to local progesterone therapy. Premenstrual all rgic rhinitis and nasal obstruction may respond to nasal drops containing 10% progeste: one. Premenstrual acne will respond to progesterone cream. However, local treatme: t is useful only in mild cases for in severe cases there are also the tension symptoms, whic: are best dealt with systemically.

PROGESTERONE THERAPY OF TOXÆMIA OF PREGNANCY

Progesterone therapy of premenstrual syndrome has opened the door to a new, and so far successful, therapeutic approach to the treatment of toxæmia of pregnancy (Dalton, 1954). The similarity of these two diseases has already been mentioned, and also the stage of symptoms which preceded the onset of signs. In premenstrual syndrome treatment is best given before the onset of symptoms or signs, so in toxæmia this is probably also the ideal; nevertheless a lapse of time has been observed in toxæmia after the onset of symptoms and before the onset of signs. Any minor symptom present during pregnancy was regarded as a possible early sign of toxæmia, and a test dose of 25–50 mg. progesterone given if any symptoms developed. If this dose removed the symptom that symptom was regarded as a possible early sign of toxæmia and continuous treatment with progesterone instituted, and if symptoms later recurred the dose of progesterone was raised until the patient again became free of symptoms.

The following cases best explain this method of treatment (*see* Fig. 3, Dalton, 1954). A housewife of 25 years, gravida 3, received progesterone for premenstrual hemicranial headaches and lethargy following her second pregnancy. At 28 weeks of her third pregnancy she complained of hemicranial headaches and bloatedness. She had gained 16 lb. in the previous four weeks and blood pressure was 145/90 mm.Hg. The test dose of 25 mg. progesterone relieved the headache for forty-eight hours but then the headache returned, so she was treated with 25 mg. progesterone on alternate days. On this dosage the blood pressure fell, and weight gain lessened and there was no recurrence of headache. She had a normal spontaneous delivery at full term.

A 34-year old housewife (*see* Fig. 4, Dalton, 1954), during her first pregnancy in 1952, was admitted to hospital at 34 weeks for toxæmia; after two weeks' bed rest she had a surgical induction, developed uterine inertia in the first stage of labour and later had a high forceps delivery. In her second pregnancy she complained of headache, spots before her eyes and nausea at 27 weeks, there were then no toxæmic signs present, but the test dose of 25 mg. progesterone brought relief of all symptoms for twenty-four hours; and she was, therefore, treated with 25 mg. progesterone daily. At 30 weeks she had a recurrence of headaches, but still no toxæmic signs; when the dose of progesterone was raised to 50 mg. all symptoms again disappeared. At 34 weeks she had a recurrence of severe headache, vomiting and spots before her eyes. It was a Monday, and the patient explained she always felt bad on Mondays, as the district nurse, who gave the daily injections, did not come on Saturdays or Sundays. Now the patient had œdema of the ankles and face, albuminuria and a blood pressure of 180/100 mm.Hg. She was treated with 150 mg. progesterone and 2 c.c. mersalyl immediately. The following day she felt better, her blood pressure had dropped and albumin disappeared but the œdema was worse. The œdema had disappeared by the third day. She remained on large doses of progesterone and continued to improve, and was ambulant throughout. At 36 weeks she developed a large urticarial weal at the injection site and as she had been symptom-free for almost two weeks the injections were stopped for one day, but on the second day there was a recurrence of headache, vomiting, and epist xis with hypertension, but no œdema. Daily injections again made her symptom-free. he had a normal spontaneous delivery at full term.

SOCIAL CONSEQUENCES OF PREMENSTRUAL SYNDROME

In view of the successful treatment with progesterone of premenstrual syndrome he social consequences merit serious consideration. There is a high incidence of crimes of violence committed by women during or immediately before the menses (Cooke, 19: 5). Will a fine or prison sentence really cure the woman, who in a sudden uncontrolled fi of premenstrual irritability, throws a rolling pin at her husband or neighbour? We h ve heard of the high accident rate among women pilots during menstruation (Whitehead, 19). Is it for the same reason that we women drivers have won the reputation for unpredicta le action on the road? During this phase of the menstrual cycle piece-time workers s: w

lowered productivity, students become mentally duller, the suicide rate is higher and untold marital unhappiness and domestic discord have resulted from premenstrual outbursts of temper and irritability.

The cost of progesterone therapy is high, but when this charge is weighed against the price in terms of human misery, suffering and injustice it is seen as a justifiable expense opening up a new vista of Medicine.

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DISCUSSION ON ANÆMIA IN GENERAL PRACTICE

Dr. D. G. French:

My contribution is a brief account of the incidence of the different forms of anæmia among 5,000 patients during the past eleven years.

Iron-deficiency anæmia is overwhelmingly the commonest form; it is difficult to give a true estimate of the prevalence of the condition, probably about 80 cases per year, of which half are associated with pregnancy.   Next in order of frequency, and forming about 1% of the total has been the macrocytic, pernicious type of anæmia, and in the period under review there have been 13 cases.   Anæmias less commonly encountered are shown in **Table I.**

TABLE I.—THE LESS COMMON FORMS OF ANÆMIA.

Chronic myeloid leukæmia	2
Acute lymphatic leukæmia	1
Banti's disease	1
Aplastic anæmia	1
Eosinophilic syndrome	1
Hypersplenic panhæmatopenia	1
Acholuric jaundice	1
Tropical sprue	1
Non-tropical sprue	1
Total cases	10

In addition, there are in the practice 4 cases of hæmophilia, 3 of them being brothers.

The conditions shown in Table I occur so infrequently that the chance occurrence of any one of them can almost be ignored, but as a group the incidence is very similar to that of pernicious anæmia.

(a) Investigation of the Anæmia

The first examination of the blood which takes about 1 hour involves hæmoglobin estimation, erythrocyte and leucocyte counts, and the preparation of a blood film which is stained and used for a general examination of the character and distribution of the cells and for a differential count of 200 leucocytes.

The reticulocyte count has an essential place in hæmatology.   Mistakes in diagnosis do occur, and the failure of treatment to produce a reticulocytosis will probably be the first indication of this.   If the reticulocyte count is not checked, it may be several weeks before one becomes certain that no real improvement is taking place, whereas failure to obtain a reticulocyte response in three or four days should cause one to re-examine the blood and to re-consider the diagnosis.

Diagnosis.—The diagnosis may be completed gradually over a period of days and by means of the methods mentioned one should be able to label the anæmia, and if it is due to iron deficiency, the cause of this should nearly always be evident.

In iron-deficiency anæmia, there is a colour-index of less than 1; the hæmoglobin level is reduced to varying degree but the erythrocyte count, which may be reduced, is more often than not within normal limits.

Anæmias with a colour-index greater than unity, in which the presumptive diagnosis is megaloblastic anæmia, should be sent to hospital for further investigation, and the diagnosis will usually be confirmed; but keep one at home and try to treat it, and you may be sure that it will turn out to be something unusual, and by that time the treatment will have rendered the diagnosis virtually impossible.

Quite commonly borderline cases are encountered with a fairly severe degree of anæmia in which the erythrocyte count and the hæmoglobin level are proportionately reduced and in which the colour-index remains close to 1. These nearly always prove to be iron-deficiency anæmia or anæmia due to depressed blood formation, rather than pernicious anæmia, and in the differentiation of these the stained film can be very useful. In such cases the outlook has been uniformly bad due to some underlying condition. In these doubtful cases, one is justified in starting treatment with iron as no interference is caused thereby, and the progress can be checked by daily reticulocyte counts: but the casual use of liver extract or vitamin B_{12} is absolutely contraindicated, as this quickly converts a megaloblastic marrow to a normo-blastic one, and it may be impossible to establish the diagnosis afterwards for some months. That, of course, is the danger and the menace of the blunderbuss preparations.

Reliance on the colour-index is a source of error when there is a combination of pernicious anæmia with iron deficiency, in which the colour-index is less than 1; but if the progress of the case is carefully watched it soon becomes apparent that the diagnosis requires re-consideration. Though such cases are extremely rare this also serves as a reminder that established cases of pernicious anæmia can become iron deficient and benefit from occasional iron therapy.

When one of the rare forms of anæmia is encountered, it may not be possible to establish the true diagnosis owing to sheer lack of familiarity, but they are fairly readily differentiated from iron-deficiency anæmia. Many are associated with considerable enlargement of the spleen which is not a feature of iron-deficiency anæmia; and if the similarity of the peripheral blood picture causes a mistake to be made, the error will soon be apparent when the case fails to respond to treatment, and no harm is done.

(b) Investigation for the Cause of the Anæmia

Iron-deficiency anæmia can never be regarded as a diagnosis; it is at best a physical sign. Take the history carefully, remembering the possibility of tuberculosis at any age; of peptic ulcer in young and middle-aged people of both sexes; of hæmorrhage following parturition, miscarriage or oft-repeated pregnancies, or of menorrhagia with or without pelvic tumour in women of child-bearing age; and of cancer somewhere, especially gastro-intestinal, in men and women over the age of 45. In the last group other common causes are rheumatoid arthritis, peptic ulcer and piles, though the patient's diagnosis of piles may in fact conceal a carcinoma of the rectum.

Idiopathic hypochromic anæmia which has recently been described in young males, and nutritional hypochromic anæmia in the aged are rare conditions, and in each the diagnosis must be reached by a process of careful exclusion.

Examination of the patient.—Some indication of the probable cause of the anæmia may have been obtained already; if not, one must conduct an examination which will include all the systems, remembering chest X-rays, also examination of hair, skin, glands, joints, and frequently also pelvic and rectal examinations. When the diagnosis is still obscure, the stool must be examined for occult blood. If there is still no indication of the probable cause of the anæmia there is no point in sending the case into hospital *at this stage*.

Treatment of the anæmia should now be started and the results checked by frequent blood examinations. I consider that the diagnosis of idiopathic hypochromic anæmia of young males, and of chronic nutritional hypochromic anæmia in the aged, should only be applied *in retrospect* to cases which have been examined and treated in this way, which have remained well after treatment and which in the fullness of time have been shown to have no serious underlying disease.

When an apparently uncomplicated iron-deficiency anæmia is effectively treated, (a) one must be able to demonstrate a reticulocytosis; and (b) the increase in the hæmoglobin level should then follow a definite pattern; if it fails to do so, the diagnosis is not completely correct, the most probable cause being some complicating factor which has not been found, and the ætiology must be re-considered. One must be perfectly satisfied in every case of iron-deficiency anæmia that the cause has been found.

Treatment of Iron-deficiency Anæmias

Oral iron therapy.—About 14% of the administered dose of ferrous sulphate is absorbed and utilized, compared with 1·5% of ferri et ammon. cit.

We have been urged to prescribe ferrous gluconate; and, more recently, ferrous succinate.

Perhaps one might add here that the general practitioner might ignore the possible ætiological significance of deficiency of the trace elements, but he should be alert to the occasional occurrence of subthyroid states.

When a patient responds satisfactorily to oral iron therapy, there is an interval of about nine days before any increase in the hæmoglobin level can be measured. After this, there is a steady return to normality at the rate of about 1% per day. The treatment of a fairly severe degree of anæmia must therefore be continued for about two months, and I do not think that the choice of preparation makes much difference. Fig. 1, which was prepared from observations made on recent cases treated with ferrous succinate, indicates the normal response to oral iron therapy.
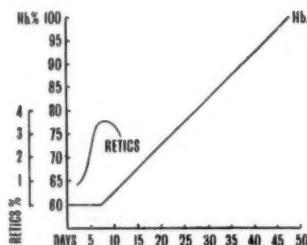

Fig. 1.—The normal response to oral iron therapy. This figure was constructed from observations made on four cases treated with ferrous succinate.

The disadvantages of oral iron therapy are that it is uncertain, because one cannot be sure that the patient is taking it regularly, and absorption is variable, especially in pregnancy where I have found the results quite unpredictable; it may not be well tolerated; and its action is a little slower than intravenous therapy, which in certain circumstances is important, for example, in late pregnancy. In general terms, the hæmoglobin level increases at rather less than 1% per day with oral iron, and at rather more than 1% per day with intravenous iron.

Intravenous iron therapy.—I use intravenous iron therapy for the majority of severe anæmias with hæmoglobin levels below 60% on account of its rapid effects, for all cases of hypochromic anæmia of pregnancy since prolonged experience of oral iron in these cases had been so disappointing, for the small minority of cases which fail to respond to oral iron therapy, and in all cases in which any part of the diagnosis is in doubt.

In 1948 I began to use Ferrevenin in the treatment of 2 cases of iron-deficiency anæmia of pregnancy, and I believe that these were the first 2 pregnant women ever to have intravenous iron therapy (French, 1948).

Administration.—In the administration of intravenous iron preparations the dangers of perivascular infiltration are very real. In my experience thrombophlebitis is extremely rare, and it probably results from failure to keep the point of the needle within the lumen of the vein, with the result that some of the material is injected into the wall of the vein, under the intima. I have tried on so many occasions to test the truth of this assertion that it has become practically a rule with me to use the same place in the vein for every injection, and I have seen no harm result. At the end of a course of injections, I can usually demonstrate the series of prick marks in the antecubital fossa in an area that could be covered by the end of a cigarette.

The injections must be given slowly; there is no doubt that the reactions which sometimes occur are to some extent related to the speed of giving the injection. The more common reaction usually appears within five minutes of the injection; the patient becomes hot, flushed and alarmed; there may be headache, a constricting pain in the chest, and, most constantly, a really severe colicky pain in the renal areas. The attack usually passes off in about twenty minutes, after which the patient feels shivery and cold. The second type of reaction resembles a vaso-vagal attack and comes on almost at once; if there is an interval the reaction is usually milder. This reaction, characterized by collapse of the patient, is more alarming and requires immediate action.

Speaking generally, one may expect to encounter a reaction when the injection is given quickly, but if the treatment is given intensively, as in some of my cases, the speed of the

injections may be gradually increased until the later ones, from about the eighth, may be given at nearly twice the speed of the earlier ones. And here is a strange thing: if there is a break for a few days in the treatment, the next injection must be given at the original rate or a reaction will occur.

It is recommended that the first dose should be 2·5 ml.; if there is no reaction, subsequent doses may be increased to 5 ml., and then to 10 ml., and it is not advised to increase the dose beyond this level.

The makers state that subsequent doses may be given at intervals, the total required quantity having been calculated from the hæmoglobin level. I prefer to give the injections daily; sometimes it suits me to give them night and morning; and I had one remarkable case in which I administered large doses three times a day.

Results of intravenous iron therapy.—Intensive treatment produces dramatic results. Subjective improvement is evident almost from the first injection, and is probably related to the raised serum iron levels.

The first objective change shown by the methods used is the appearance in the peripheral blood of increasing numbers of reticulocytes, and there is a significant increase in the reticulocyte count on the third day, though my most intensively treated case had a significant reticulocytosis forty hours after the start of treatment. The reticulocyte peak usually occurs about the fifth day, but it may be delayed until the eighth day, and is most commonly about 8 to 10%, though the actual magnitude of the increase appears to have little clinical significance.

The interval between the start of treatment and the first undoubted and significant increase in the hæmoglobin level varies from five to nine days; thereafter there is a steady return to normality which is reached about five weeks later, depending to some extent upon the original starting level. The first significant increase in the erythrocyte count is observed about ten days after starting treatment, and this returns to normal more rapidly than the hæmoglobin level; in fact there is frequently a period about four weeks after the start of treatment during which counts between 5,000,000 and 6,000,000 are not uncommon, and this would seem to indicate that the formation of new erythrocytes was taking place at a rate in excess of the destruction and removal of effete cells (Fig. 2).
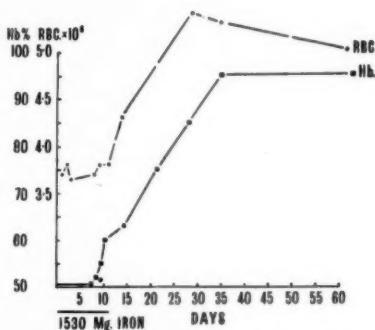
FIG. 2.—The normal response to intravenous iron therapy administered daily. Abnormally high erythrocyte counts are commonly observed four or five weeks after the start of treatment, as production proceeds at a greater rate than destruction.

Failures.—In the beginning, cases were encountered in which the results did not quite come up to expectation; for example, in cases in which the anæmia was due to repeated hæmorrhage and in which the hæmorrhage continued during treatment. And later it was noticed that the anæmia associated with rheumatoid arthritis did not respond fully. But there was a residue of apparently healthy persons in whom physical examination was completely negative, whose blood condition did not return to normality.

The following is a brief outline of 5 such cases. 2 were young people aged about 19; about three years later mass miniature radiography revealed that they had pulmonary tuberculosis with cavitation. Another was a woman of 55, and three months later she developed intestinal obstruction due to an annular scirrhous carcinoma of the colon. A man of 63 developed a perforation of the gall-bladder nine months later; he was operated upon but died. Another man of 59 developed retention of urine a year later, and was found to have an inoperable carcinoma of the prostate.

In the light of these and similar experiences, I now take the view that iron-deficiency anæmia in an apparently healthy person, which fails to respond fully to intravenous iron therapy in correct dosage, has some undiscovered serious cause for which an intensive search must be made. In actual practice, one can be sure in about three weeks that the hæmoglobin curve is lagging behind the normal expectation and that something is wrong. I have described this in greater detail elsewhere (French, 1953).

The hypochromic anæmia of pregnancy.—During pregnancy a physiological hydræmia occurs, and this causes a reduction in the erythrocyte count and hæmoglobin level when estimated by ordinary methods. Now, when iron deficiency is superimposed on these physiologically reduced levels, a major difficulty becomes apparent. The hydræmia is not constant either from patient to patient, or in the same patient for the duration of the pregnancy. Is there, then, a critical hæmoglobin level at which one can differentiate between a physiological anæmia and one due to iron deficiency?

With the introduction of Ferrivenin, much of the earlier difficulty was solved. It became evident that oral iron therapy during pregnancy is unsatisfactory and the results unpredictable.

The next step was one which had held me up on more than one occasion in the days of oral iron therapy. This objective was to obtain a clear picture of the fluctuations which occur in the erythrocyte counts and the hæmoglobin level during pregnancy and the puerperium in the known absence of iron deficiency; in other words, to create an ideal of normality which would be a standard against which future cases could be judged. Without this, what is meant by anæmia in pregnancy? Yet, so far as I am aware, this approach to the subject is unique.

To obtain this information, I selected 5 perfectly healthy young primiparæ, who had no evidence of anæmia so far as I could ascertain, and who lived in perfectly satisfactory home conditions. They were all given injections of intravenous iron in amounts calculated purely from their hæmoglobin levels, without reference to the fact that they were pregnant. This treatment produced no change in the blood pictures, and in no case was there a reticulocytosis. I then felt justified in assuming that these women were not iron-deficient, and went on to make frequent observations on their blood during pregnancy and the puerperium. Fig. 3 is the record of one of these cases. The means of the observations of all 5 cases are shown in Fig. 4.
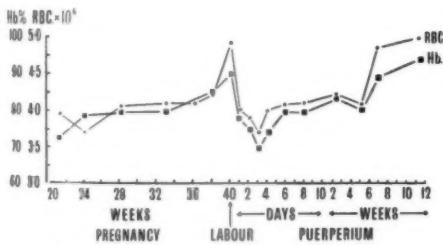
Fig. 3.—Normal fluctuations in the erythrocyte counts and hæmoglobin levels during pregnancy and the puerperium in healthy primiparæ in the absence of iron deficiency.
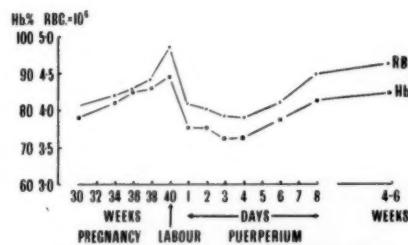
Fig. 4.—Similar to Fig. 3, but representing the means of observations on five non-anæmic primiparæ.

The significant points in Fig. 4 are these:

(1) There is a reduction in the erythrocyte count and hæmoglobin level during the greater part of pregnancy, and this is physiological.

(2) As would be expected, this is uninfluenced by iron therapy.

(3) The lowest values are found between the 20th and 30th week (in one of these cases, a hæmoglobin level of 65% was observed on three occasions during this period); there is then a very gradual rise until about the 35th week, after which the increase in both values is rapid and continues until the onset of labour when values closely approximating to normal non-pregnant levels are observed.

(4) After labour, there is a rapid fall in both values on the first day of the puerperium; this fall continues more gradually for a further two or three days, when values similar to the lowest pregnancy levels are reached; thereafter there is a steady return to normality which is reached in six to eight weeks.

(5) The two curves remain close together, which indicates that the colour index remains close together to unity.

In addition to the injections of intravenous iron and the checking of the results by reticulocyte counts, the results of 146 hæmoglobin estimations and 127 erythrocyte counts are incorporated in Fig. 4.

It is made clear by Fig. 4 that a statement of the hæmoglobin level is only of value when the stage of pregnancy is indicated. And also that it is patently fallacious to judge the efficacy of any form of therapy when hæmoglobin estimations made during the last month of pregnancy or the first month of the puerperium are included. When the hæmoglobin level is the only criterion adopted, as it so often is, it could equally well be argued that any outlandish form of therapy is a cure for anæmia, as the hæmoglobin level is subject to a very considerable physiological increase during these periods without any treatment whatsoever. Similarly, any efforts to raise the hæmoglobin level during the early months of pregnancy in the face of a developing hydræmia must surely account for some of the so-called failures.

Treatment of the hypochromic anæmia of pregnancy.—Finally, I wish to show the results of intravenous iron therapy in the hypochromic anæmia of pregnancy, in two typical cases.

The findings shown in Fig. 5 relate to a primipara aged 21 years, who was 27 weeks preg-
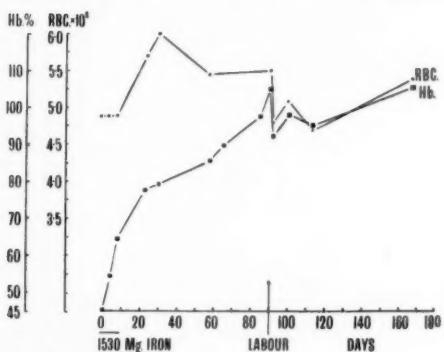
FIG. 5.—The hypochromic anæmia of pregnancy treated with intravenous iron.
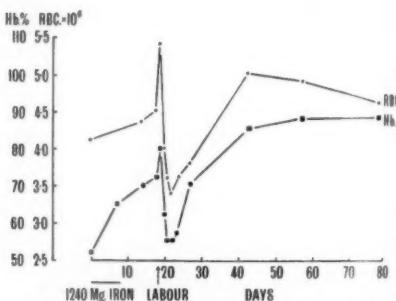
FIG. 6.—Hypochromic anæmia of pregnancy treated with intravenous iron. Differs from Fig. 5 in that treatment was started very late in pregnancy.

nant. The findings were: R.B.C. 4,900,000; Hb 45% (Sahli); colour-index 0·46. The low colour-index is represented on the figure by the wide separation between the curves representing the erythrocyte counts and the hæmoglobin levels. She was treated by the intravenous administration of the equivalent of 1,530 mg. of elemental iron, spread over ten days. Thirty-two days after the start of treatment, when she was 31 weeks pregnant, the erythrocyte count was 6,000,000. The hæmoglobin level increased rapidly, and thirty days after the start of treatment was 80%. The colour-index returned to normality more slowly over a period of eighty days.

The next case (Fig. 6) was a multipara, 37 weeks pregnant. The findings were: R.B.C. 4,100,000; Hb 52% (Sahli); colour-index 0·63. She received the equivalent of 1,240 mg. elemental iron by intravenous injection during the next seven days. The rate of improvement was rapid, and in the early puerperium, thirty days after the start of treatment, blood levels within physiological limits had been attained. The day before the onset of labour, the findings were: R.B.C. 4,500,000; Hb 72%; colour-index 0·80; these levels, achieved in eighteen days, are almost physiological.

Speaking generally, the hæmoglobin level in pregnancy is restored to within normal physiological limits by means of intravenous iron therapy within five weeks. The colour-index returns to unity more slowly, as it depends to some extent upon the rate of removal of "anæmic" effete erythrocytes, cells which must be included in a count but which contain very little hæmoglobin. For this reason, the colour-index, which is so valuable in diagnosis, lags too far behind to have a similar value as a criterion for the effectiveness of treatment.

I have mentioned that a hæmoglobin level of 65% (Sahli) was observed on several occasions in one of my non-anæmic cases. Attempts are constantly being made to fix some arbitrary hæmoglobin level as a standard for anæmia in pregnancy, and I am convinced that this cannot be done. The fluctuations due to hydræmia are such that any chosen hæmoglobin

level down to 65% will be observed at two periods in pregnancy: once during the early months when values are falling, and again during the last month when values are rising; and no single hæmoglobin level can indicate the presence of anæmia at all stages of pregnancy. In all these physiological fluctuations, the colour-index remains fairly stable, and should be far more extensively used than hæmoglobin levels as a guide to the presence or absence of iron-deficiency anæmia in pregnancy.

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Dr. M. C. G. Israëls:

Iron-deficiency anæmia can nearly always be dealt with by the practitioner himself; patients need only come to hospital if the cause of their anæmia is in doubt, particularly if malignancy is suspected as the cause of the anæmia.

So I will confine myself to considering how the other anæmias are best managed in practice.

The patient will have had a blood count and I am taking it for granted that physical examination has excluded such things as grossly enlarged spleen, enlarged lymph gland masses, abdominal tumours.

If the colour-index is less than 1·0, iron-deficiency anæmia is the answer. If it is about 1·0, the conditions in Table I are those to be considered. Iron-deficiency anæmia with

TABLE I.—COLOUR-INDEX ABOUT 1·0	TABLE II.—COLOUR-INDEX OVER 1·0
Iron-deficiency anæmia	Pernicious anæmia
Malignancy (alimentary tract especially)	Leukæmia, aleukæmic forms
Reticuloses (including Hodgkin's disease)	Acquired hæmolytic anæmia
Uræmia	Sprue, and non-tropical steatorrhœa
	Aplastic anæmia

body fluid dilution, as for example in pregnancy, can present with a C.I. about 1·0. But the possibility of other causes is much more likely with a normochromic anæmia and they should be excluded. To do this, out-patient hospital investigation is necessary. Alimentary tract malignancy can be very difficult to demonstrate, especially tumours affecting the fundus of the stomach. The reticuloses are liable to be deceiving when the mediastinal glands or the abdominal glands are the only areas affected. Uræmia can be astonishingly silent, and the first sign may be anæmia perhaps with some epistaxis. The prognosis is always bad in patients who present with anæmia as a first sign of kidney failure.

If the colour-index is over 1·0 quite a different set of conditions must be thought of (Table II). Pernicious anæmia is the most obvious. But it is bad practice to give liver, vitamin B_{12}, or any similar compound to patients merely because they have a hyperchromic anæmia. The other diseases in this list need quite different treatment, and giving the wrong treatment to a patient with hyperchromic anæmia may greatly confuse the diagnosis because a very important piece of information in the differential diagnosis of this group is the state of the bone-marrow. In pernicious anæmia the marrow is megaloblastic; in leukæmia the marrow shows large numbers of abnormal and primitive leucocytes even though these are not to be found in the peripheral blood. In acquired hæmolytic anæmia the marrow is normoblastic, and in sprue the marrow will be megaloblastic in patients with hyperchromic anæmia. In aplastic anæmia the marrow may be very hypocellular with mostly lymphocytes, or it may show some erythroblasts, mostly mature normoblasts.

When no treatment has been given, megaloblasts and normoblasts are quite distinct from typical cases but exhibition of B_{12} or folic acid or liver, alone or in mixtures, causes megaloblasts to change over to normoblasts. In relatively early cases of pernicious anæmia and quite a few of steatorrhœa, there may only be partial megaloblastic changes in the nuclei of the erythroblasts. These transitional megaloblasts are more easily covered up by treatment.

So, unless there are very good reasons, any suspected pernicious anæmia patient should be sent for marrow examination before treatment is given. After all, the patient is being condemned to life-long treatment, and it is surely worth while having the diagnosis firmly established.

If the patient will not go to the hospital or laboratory, then a sore tongue with a lemon-yellow colour, flatulent indigestion and paræsthesiæ, in the absence of significant enlargement of the spleen or lymph glands, or abdominal mass, can be taken as a clinical picture of pernicious anæmia, and treatment with cyanocobalamin can be given. But if the patient does not respond, the trail has been muddled.

It is for this reason that both Dr. French and I are so insistent that no one should u.. the hæmatinic mixtures that are so powerfully advertised. If patients need more tha.. one hæmatinic, they should be prescribed separately.

In the differential diagnosis of hyperchromic anæmia the diagnosis of leukæmia .urns almost entirely on the examination of the bone-marrow.

Acquired hæmolytic anæmia is more difficult. Patients often present a lemon-y..llow pallor. The spleen is often, but not always, much enlarged. In the blood a pers.stent reticulocytosis is present, significant if no treatment has been given, and the marr.w is normoblastic throughout. The Coombs antiglobulin test is nearly always positive and is a valuable confirmation of the diagnosis.

Sprue and steatorrhœa are very likely to be the cause of hyperchromic anæmia in young adults, an age when pernicious anæmia is very rare. If severely anæmic, a true megalo-blastic marrow can be found. But free HCl is usually present in the gastric juice. A properly carried out fat balance shows less than 90% absorption with a 70-gram fat diet. These patients respond to folic acid, rarely to vitamin B_{12}. They need control of the fat and starch in their diet.

Aplastic anæmia is obvious enough when a young woman appears bleeding from mucous membranes with depression of all the elements of the blood. But there are less severe grades that can be very deceiving and they occur most often on the older age groups, 50 and upwards. They often show a hyperchromic blood picture. The marrow is less cellular than usual; there is depression and relative maturity of the erythroblasts and granulocytes; there are no megaloblasts. These patients will not respond to hæmatinics, and only blood transfusion does them any good. But they are worth trying to treat this way on an out-patient basis as useful life can often be prolonged for many years.

Table III shows a summary of the treatment of the different forms of hyperchromic anæmia,

TABLE III.—TREATMENT OF HYPERCHROMIC ANÆMIAS

Disease	Treatment
Pernicious anæmia	Vitamin B_{12} (cyanocobalamin)
Leukæmia, subleukæmia	Cortisone
Acquired hæmolytic anæmia	Cortisone or splenectomy
Sprue, steatorrhœa	Folic acid and diet
Megaloblastic anæmia of pregnancy	Folic acid
Aplastic anæmia	Blood transfusion

and it will be seen how important it is to get the diagnosis right before the start of treatment.

Anæmia of Pregnancy

Here I shall consider only the megaloblastic anæmia of pregnancy. Regular bone-marrow examination of patients whose anæmia does not respond to parenteral iron treatment has shown that some degree of megaloblastic anæmia is much more frequent than was suspected. But megaloblastic anæmia of pregnancy is still much less common than the occurrence of a high colour-index in pregnancy would lead us to expect. In fact, no reliance can be placed on the colour-index in pregnancy; this is because of the serious changes in the balance between red cell mass and plasma volume. A high colour-index often occurs when this dilution disturbance is present, and it does not mean a megaloblastic anæmia, which implies an anæmia with hæmoglobin less than 9 grams/100 ml. (70%) that will not respond to parenteral iron. There may be other significant clinical signs, like sore tongue. The diagnosis is settled by examination of the bone-marrow. It is typical of the condition that many erythroblasts are the so-called "transitional" megaloblasts. These patients ca.. be very ill with unpleasant mouth lesions and grave anæmia.

Folic acid is the correct treatment and for quick results it can be given intravenous.y in a dose of 100 mg. A daily oral dose of 20 mg. should be continued throughout the pregn..ncy and for one month afterwards. Such patients should come to hospital for investigatio.. as soon as it is clear that they are becoming anæmic and do not respond to simple measur..

If Dr. French's figures are typical, general practitioners do not see hyperchromic ana..nia very often. All the more reason for sending them for proper investigation as soon as ..os-sible, and for sending them untreated. If the patient has had some treatment, then .. is essential to inform the hospital physician exactly what has been given. With this p..cy, management of the hyperchromic anæmias should be a source of satisfaction rather tha.. of frustration to the practitioner.

JOINT MEETING No. 1

Section of General Practice with Section of Medicine

Chairman—R. J. MINNITT, M.D., F.F.A. R.C.S., F.R.C.O.G.
(President of the Section of General Practice)

[*November 24, 1954*]

DISCUSSION ON THE USE AND ABUSE OF ANTIBIOTICS

Dr. David Wheatley: *Uses of Antibiotics*

Until recently, as far as the general practitioner was concerned, antibiotics could be divided into two groups, those which were freely prescribable and those which could only be obtained through the hospital service. In the first group are penicillin, streptomycin, chloramphenicol, erythromycin and the sulphonamides, for the last-mentioned are no less an antibiotic than the others and must be considered in conjunction with them. In the second group are the tetracyclines (Aureomycin, Terramycin and tetracycline itself), the polymyxins and a heterogeneous medley tailing off in practical usefulness. Erythromycin may be dismissed immediately except for the rare case of infection resistant to all the other antibiotics. When indicated, at the present time it is probably better to use an antibiotic from the second group in preference to erythromycin, because of the latter's strong capacity for inducing drug resistance. However, as in the case of penicillin, time may show this to be a false fear as far as general practice is concerned, but it must be remembered that erythromycin covers only the same bacterial spectrum as penicillin itself. Likewise there will be little indication to use streptomycin alone because of its ototoxicity, although the risk of the latter may be reduced by using a streptomycin-dihydrostreptomycin mixture. I am not including the treatment of tuberculosis as this is usually undertaken by the chest clinics. This leaves penicillin, the sulphonamides and chloramphenicol which have been our mainstay in general practice, until the recent release of the newer antibiotics.

Sometimes it may be expedient to combine two antibiotics, and here it should be remembered that antibiotics may be divided, roughly, into two groups. The first includes penicillin, the sulphonamides and streptomycin, all of which are synergistic with each other. The second group includes chloramphenicol, Aureomycin, Terramycin, &c., these also being synergistic one with the other. Members of one group, however, are antagonistic to members of the other and should not be combined.

As bacteriological examination may often be delayed, some reliance must be placed upon "blind" therapy. Table I shows some of the commoner bacteria with their degrees of sensitivity to different antibiotics.

TABLE I.—BACTERIAL SENSITIVITIES

	Sulphonamides	Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Terramycin
Staph. aureus	+	++++	++	++	++	++
Str. hæmolyticus	+++	++++	−	++	+++	++
Pneumococcus	+++	++++	++	+++	+++	++
H. pertussis	−	−	−	++	?+	?+
Bact. coli	+++	−	+++	+++	++	+++
Bact. sonnei	+++	+	+	+++	++	+++
Neisseria	+++	++++	−	++	++	++
Proteus	−	−	+	+	−	?
Pseudomonas	−	−	?+	?+	?+	?

We are now in a position to decide which antibiotic or combination of antibiotics is most suitable for each infection and Table II shows some of the commoner conditions met with in general practice. In each case the antibiotic of choice is shown, together with the next most suitable one. If there is no response within thirty-six hours, the second choice should be substituted, or whatever other antibiotic may be indicated as a result of bacteriological examination and sensitivity tests.

Mode of administration.—Frequent injections are clearly impossible in general practice, therefore in the case of penicillin, reliance must be placed upon twelve- or twenty-four-hourly injections, or upon oral therapy. Hence we have here a major difference between domiciliary and hospital practice, as the widespread use of oral penicillin is almost entirely confined to general practice. Hence the general practitioner is in a more favourable position to form an opinion as to its effectiveness.

Three of the more common conditions are (1) Minor Pyogenic; (2) Acute Tonsillitis and Pharyngitis; (3) Acute Otitis Media.

TABLE II

(1) *Chest Diseases*					(6) *Obstetrics and Gynæcology*			
Pneumonia	P+S	(C)			Carbuncles, boils, &c.	P	(C)	
Acute bronchitis	P	(S)			Burns	P+Str.	(C)	(topical)
Pleurisy	P				Puerperal fever	P+S or Str.		
(2) *Infectious Diseases*					Mastitis (infective)	P	(S)	
Dysentery	S	(C)			Vaginitis (bacterial)	S	(C)	
Pertussis	C				Infected nipples	P+Str.		(topical)
Scarlet fever	P				(7) *Dermatology*			
Gonorrhœa	P				Cellulitis	P	(P+S)	
(3) *Genito-urinary Infection*	S	(C)			Impetigo	P		(topical)
(4) *E.N.T. Infections*					Erysipelas	P	(P+S)	
Acute otitis media and acute mastoiditis	P+S	(C)			Intertrigo	C	(P)	(topical)
Chronic otitis media	C	(topical)			(8) *Ophthalmic Conditions*			
Meatal boils	P				Conjunctivitis	P	(C)	
Acute tonsillitis and quinsy	P	(S)			Blepharitis	P	(C)	(topical)
Acute sinusitis	P				Corneal ulcers	P		
(5) *Minor Surgical Conditions*								
Hand infections	P	(C)						

Key

S=Sulphonamides   C=Chloramphenicol   P=Penicillin   Str.=Streptomycin

(1) *Minor Pyogenic Conditions*

Boils, carbuncles, abscesses, whitlows, infected injuries, &c. These conditions provide a constant stream of surgery attendances. They must be treated with penicillin by injection. My own experience with oral penicillin in these conditions, even in individual doses of two million units, has been extremely disappointing, apart from the occasional mild case in a child. A high blood penicillin level is necessary to ensure penetration of the antibiotic into the localized inflammatory focus.

There are two alternatives: Aqueous sodium penicillin G in twelve- or twenty-four-hourly dosage or a long-acting repository preparation. Over the past seven years I have treated the majority of these cases with four or five daily injections of 200,000 or 500,000 units of aqueous sodium penicillin G. Surgical intervention is hardly ever necessary although very occasionally an alternative antibiotic has to be used because of the presence of resistant organisms. I give my penicillin by subcutaneous injection, as this is simple, time-saving and painless, particularly in the case of children. A dose of 500,000 units dissolves readily in 1 ml. of sterile water and, apart from occasional transient stinging and slight bruising at the injection site, it is free of side-effects. I have now given many thousands of such injections without any other reaction. Several workers have shown absorption to be exactly the same, if not superior, after subcutaneous injection as after intramuscular injection. Custom dies hard and I believe that in hospital penicillin is still given by intramuscular injection, although with penicillin in its present highly purified state, it is difficult to see the justification for continuing this. Fig. I shows a typical result in a case of carbuncle of the neck, using this treatment.

A   B
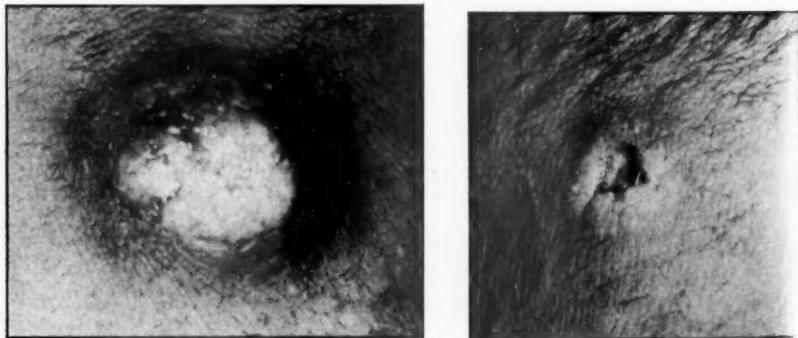
FIG. 1.—First day—before treatment with subcutaneous penicillin. Tenth day—after daily injection of 500,000 units for five days.

Recently I have treated a series of 40 cases, with a single injection of long-acting bene-thamine penicillin (600,000 units). This has obvious advantages, if equally effective, as it reduces surgery attendances by three-quarters. A disadvantage is the intramuscular injection which in 20% of cases produces pain, sometimes so severe as to incapacitate the recipient for several days. The results too, are less certain. Thus in these 40 cases, there were 10 complete failures, which subsequently responded rapidly to daily aqueous penicillin and 2 cases in which resolution was prolonged. The other 28 cases resolved rapidly in the usual five to eight days. I would like to contrast this with a series which I published in 1949 (*Practitioner*, **162**, 508) of 43 similar cases treated with 4 daily subcutaneous aqueous penicillin injections of 200,000 units. There were no failures, and only one case of delayed resolution.

(2) *Acute Tonsillitis and Pharyngitis*

I treat all these cases with oral penicillin, when they are clearly infective rather than catarrhal. For adults I use 250 mg. (400,000 unit) tablets of unbuffered penicillin G in a standard dose of 2, eight-hourly on an empty stomach. This conveniently fits into the waking day, the first dose being taken before breakfast, the next between 3 and 4 p.m. and the last one on going to bed. I have found from experience that patients with a non-serious condition just will not stick to six- or four-hourly dosage at night. This eight-hourly regime I have found to be entirely effective. Usually there is a striking improvement within eighteen hours with fall of temperature to subnormal and relief of soreness. Occasionally a case fails to respond. This is usually due to infection with a non-sensitive organism and if there is no response within thirty-six hours, therapy should be changed to sulphonamides or Chloromycetin, whilst the result of bacteriological examination is awaited.

In children, it is convenient to use one of the long-acting dibenzyl penicillin suspensions. Their palatability and high concentration (300,000 units/fl. drachm) make them particularly suitable for this purpose. Recently I have been observing the effects of doses given morning and evening only; the dose for 5-year-olds being 600,000 units b.d. So far, in 22 cases exhibiting acute follicular tonsillitis with temperatures in the region of 102-3° F., there has been complete resolution of symptoms and signs in forty-eight hours in every one. Treatment is usually continued for three to four days. Quite apart from the curative effect of such a method, it is very probable that it exerts untold prophylactic benefit in preventing the serious sequelæ of streptococcal infection. Thus in my practice over the last seven years, I have seen no cases of acute rheumatism or acute nephritis and only 3 cases of scarlet fever, all of which had developed before treatment could be instituted.

(3) *Acute Otitis Media*

In contrast to the low incidence of streptococcal allergy in my practice, acute otitis media is extremely prevalent. This occurs either as an acute entity or secondary to untreated throat infection. Often the infection is mixed, and penicillin alone is usually inadequate to deal with it. Oral penicillin, in the doses already outlined, however, may be readily combined with sulphadimidine, also in eight-hourly dosage, and this synergistic combination will deal with the majority of infecting organisms. Thus in a series of 61 cases (*Brit. med. J.*, 1953, i, 806), every case resolved with either oral penicillin or penicillin+sulphadimidine. Oral penicillin alone proved sufficient in the milder cases, in which inflammation and bulging of the tympanic membrane were present, but little constitutional disturbance. In severe cases, with much pyrexia and pain or when perforation had already occurred, the two drugs were given together. Of 29 cases treated with oral penicillin alone, none perforated after treatment was begun and there were no recurrences in the next three months. In one case, chloramphenicol was substituted because of lack of response. Of 32 cases treated with oral penicillin and sulphadimidine combined, 13 had perforated before treatment was begun. All these perforations healed and there were no other instances of perforation. One case suffered a recurrence in three months and in 2 other cases chloramphenicol had to be sub-stituted because of lack of response.

General practice offers unique opportunities for follow-up of these cases, with particular reference to the late effect on hearing. About three-quarters have been observed for periods of two to four years and in none has there been any residual hearing defect, as measured by the ability to hear the whispered voice at 15 feet with the affected ear alone.

Professor L. P. Garrod: My part in this meeting is also to speak on the use, as distinct from the abuse, of antibiotics, and the aspects of this large subject with which I hope to deal can be stated in a few propositions.

The first is that penicillin, when it will serve the purpose, is the antibiotic of choice. The decision to use it is perhaps more easily made than the choice of many forms of this drug which are now available. Sodium penicillin produces high blood levels lasting only a few hours, and procaine, benethamine and benzathine penicillin act respectively for about one,

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four and twenty-one days after a single moderate dose, but produce proportionately lower blood levels. A very long-acting form is of obvious value in the prevention of rheumatic fever and in the treatment of highly susceptible infections, such as yaws, in patients who may not return for a second dose. What is much less certain is the relative advantage of high intermittent blood levels or continuous low ones in the treatment of everyday conditions. Some important theoretical considerations involved in this are often overlooked, and the question is not only more complex than is generally thought, but still unsettled.

My second proposition is that, as regards choice of treatment, infections fall into two classes. There are those in which the choice of the antibiotic follows automatically from the diagnosis: these are specific diseases of which the bacterial cause is always the same and always susceptible to the antibiotic in question. They include all characteristic hæmolytic streptococcal infections, syphilis, typhus, typhoid and plague. In the other class are conditions in which the nature of the infection does not follow from the clinical diagnosis, and those, such as a carbuncle, in which it does, but the sensitivity of the organism to a given antibiotic cannot be assumed. In all such patients treatment should if possible be based on bacteriological examination including a sensitivity test; only then can it be pursued with confidence in the result. The chief types of organism whose sensitivity to antibiotics is unpredictable are staphylococci and various Gram-negative bacilli, and the tendency is towards an increasing frequency of strains resistant to any antibiotic which has been in general use for any considerable time.

Of the newer antibiotics two have very restricted but nevertheless valuable uses. Neomycin is generally considered too toxic for parenteral use, but given orally it is preferable to streptomycin for pre-operative suppression of the bowel flora. Its advantages are that bacterial resistance to it is less readily developed, and that in any case such resistance is distinct from that to streptomycin, so that it leaves the field clear for the later use of that drug should it be indicated. If applied to the skin, as it sometimes is, neomycin has the further advantage of not sensitizing the patient to streptomycin. Polymyxin finds its clearest indication in serious infections due to *Ps. pyocyanea*, an organism which is apt to be resistant to all other drugs whatever. *Bact. coli* is also highly sensitive to it, as are other related species. Meningitis due to such organisms can be safely treated by intrathecal, and urinary infections by intramuscular, injections of polymyxin B or E. These two forms of this antibiotic, of the five now known, do not cause renal damage if used in moderation.

Erythromycin has a very similar antibacterial spectrum to that of penicillin, particularly in relation to Gram-positive cocci: their differences in action on certain Gram-negative bacilli are somewhat more pronounced, and the degree of effect against such organisms is, of course, much less. Erythromycin is an easy alternative to penicillin for any pyogenic coccal infection in which penicillin is contraindicated on account of bacterial resistance or sensitivity in the patient. The only infections in which bacterial resistance—not only to penicillin but to the tetracyclines—are likely to call for its use are staphylococcal. In my opinion it should be used with caution and restraint for this purpose, and caution in hospital should go to the length of isolating the patient with a staphylococcal infection as for infectious disease. Resistance to erythromycin can develop rather rapidly, and since this antibiotic is now our last line of defence against staphylococcal infection, every effort should be made to prevent the dissemination of resistant strains.

The latest important antibiotic—tetracycline—is almost indistinguishable from chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) in its antibacterial action: such superiority over them as it possesses depends on a lesser liability to cause gastro-intestinal disturbance. It seems evident from observations in the U.S.A. that tetracycline less often causes nausea or diarrhœa than either of these other drugs. On the other hand, it is difficult to understand why its use should not sometimes be complicated, as is that of the others, by a fulminating enteritis caused by a staphylococcus resistant to all of them.

My final proposition is that combined treatment is being too freely used. It has several distinct theoretical advantages, but the application of each is limited. Synergism is one, but the synergic action of penicillin and streptomycin is therapeutically essential perhaps only in endocarditis due to *Str. fæcalis*. Some combinations are actually antagonistic, and clear clinical proof of this has been obtained in the much inferior results when chlortetracycline was given in addition to penicillin in pneumococcal meningitis. The combination most commonly used, because it has been widely advertised as a commercial product, is that of penicillin and streptomycin. The great majority of patients to whom this has been given would have done equally well with penicillin only, and there are several good reasons why streptomycin should not be employed except for clear indications.

Dr. Lindsey W. Batten: I take it that by "abuse of antibiotics" we mean "misuse" and that we are concerned with well-intended but harmful employment of these agents. Every abuse of antibiotics contravenes at least one of three principles or rules of good practice.

Toxicity.—The first is not to hurt or endanger our patients—*primum non nocere!* It is certain that many patients have been hurt—some mortally—by antibiotics and I am sure that many patients and some doctors are unconscious of the risks they take when they receive or give these things.   We here know that all antibiotics except penicillin can be toxic (though you would never think so from the advertisements).   We can deduce that on this particular count penicillin is best and that antibiotics, like sulphonamides, are, in general, short-term, and not long-term remedies.   There I will leave toxicity—perhaps the least disturbing of the dangers, for other things that *can* happen are quite terrifying.

May I briefly recall a few recent happenings, courageously reported in the recent literature?

On March 27, tetracycline got this modest welcome in an Annotation (*Lancet*, 1954). "It is valuable to have a broad-spectrum antibiotic which seems to cause unpleasant side-effects so seldom".   On May 8, Hay and Mackenzie (1954) reported the deaths of two young children from fulminating staphylococcal gastro-enteritis on the fifth and sixth days of treatment with oxytetracycline (Terramycin).   One, a girl of 6, was a salmonella carrier but "physically well" when treatment began; the other, a boy of 2, was recovering from a mild diarrhœa believed, on indirect evidence, to be Sonne dysentery.   These tragedies and misadventures are disturbing enough but in our daily practice the use of oxytetracycline, at least for minor illness, should not be hard to avoid.   It is otherwise with penicillin which, I am sure, has seemed to most of us until quite lately surprisingly safe.   It is not so.

Last January R. C. Bell (1954) reported two sudden deaths and some near-fatal anaphylactic reactions after what was at least meant to be intramuscular injection of procaine penicillin.   A child of 3½ received one dose safely but died two and a half hours after the second injection next day.   The condition for which it was given is not reported.

A man with thrombophlebitis had a severe anaphylactic reaction after Distaquaine—given once before with a mild reaction.   His life was saved with adrenaline but it was a near thing.   Other similar cases, very alarming to read, are reported in the same communication.

Nor is it always procaine penicillin.   A man with a stricture was given, as prophylaxis, a dose of penicillin G before a bougie was passed.   He had had many such injections safely before—some trouble once with procaine penicillin—but this last injection proved fatal.

Quite lately W. J. S. Still (1954) reported from Durham the case of a young woman of 28 who was given 300,000 units of crystalline penicillin by injection for a small whitlow in the second day of her puerperium.   Twenty-four hours later, besides pain, redness and swelling at the site of injection, she had symptoms as of "acute abdomen".   Laparotomy disclosed 6 in. of small bowel, dark purple and apparently becoming necrotic.   This was resected and after a stormy post-operative period with severe anaphylactic phenomena in many parts of the body she recovered.   After—but not before her injection was given— it was discovered that she had reacted unfavourably to penicillin some years before.   Still gives references to fatal anaphylactic reactions reported in the *British Medical Journal* by various authors in 1951, 1952 and 1953.

One case of another kind was reported by S. G. Browne (1954).   Briefly, a patient in the Congo with amœbic hepatitis received, in addition to the specific treatment for amœbic infection, a total of 6½ million units of penicillin.   On the last day of his penicillin he began a moniliasis of the air- and food-passages which refused to be subdued either in Africa or in London and was still active four years later.

Though these happenings are obviously not cases of abuse they are clear evidence that the antibiotics, emphatically including penicillin, are dangerous—far more likely to end a life suddenly and unintentionally than most of the drugs in the schedules of the D.D.A.   To employ them without recognizing this fact, to give them without all reasonable and practicable precautions is, I suggest, to abuse them.

What can be done to prevent recurrence of such incidents?

Hay and McKenzie (1954) most reasonably suggest that "Broad spectrum antibiotics should not be used in minor illness".   If a healthy child's bowel cannot be cleared of salmonella or Sonne by safer means, well, carry them she must.   If I can find no other way to rid a young woman of axillary boils than to give her the erythromycin which alone controls her staphylococcus, then I must urge her to put up with them.   (In parenthesis, judicious X-rays cured her.)   Procaine penicillin may get into veins by mistake, though it seems pretty certain that this is not always the cause of the trouble.   Bell, Rannie and Wynne (1954) suggest means to reduce the risk, not elaborate but hard to use invariably in busy general practice.   Without going all the way we could, I think, always inject into the upper buttock and always leave the needle in situ for some seconds after the stab, to make sure no blood comes out through it, before we attach the charged syringe.

We must always ascertain our patient's previous experience of penicillin before we inject it; have adrenaline or antihistamines handy and, I suggest, use no procaine penicillin if crystalline will serve and no antibiotic if sulphonamides will do as well.   We should think twice about giving the "first ever" dose of penicillin—in itself the safest of all but possibly

sensitizing. The "penicillin umbrella" should be reserved for real impending storms and not unfurled and hoisted at every threatened shower.

Wastage.—Some may say that wasting is merely an economic sin. I cannot agree.

Economy—the nice adjustment of means to ends—pertains, I am sure, to the καλὸν κ'ἀγαθὸν—the beautiful and good. Waste, its opposite, pertains to the διογρόν και κακόν—the ugly and bad. I can adduce no evidence that antibiotics *are* wasted.

The Medical Research Council (1954) published the results of a trial of systemic antibiotics in certain dermatoses. The substances included Aureomycin, chloramphenicol and Terramycin and they proved useless for herpes simplex recurrens, dermatitis herpetiformis, pityriasis rosea, lichen planus, discoid eczema and plantar warts. I cannot believe the M.R.C. would have conducted this research had not many practitioners thought these might possibly be of benefit. Chloramphenicol has no effect on whooping cough after the first week and it has no very startling effect even then. Its occasional use may be justifiable but I feel myself that even if it could not cause aplastic anæmia the use as a palliative of so very costly a remedy in an illness often no worse than a nuisance comes perilously near to abuse.

Then there is oral penicillin. Anyone who dislikes stabbing children must want to believe in its efficacy but the finding of Fairbrother and Daber (1954) last April that "absorption was irregular irrespective of the nature of the compound and the age of the recipient" rings true to me and I cannot help thinking it is abuse on the score of waste and futility to give it as a first dose in acute infection and doubtful practice to give it to adults at all.

Penicillin lozenges I think may constitute an abuse by merely existing.

The third, most subtle and, in the long run, probably worst abuse is queering the pitch for our successors—or even for ourselves if we go on playing. Those deadly staphylococci, those monilia in permanent possession of the field are not pirates or privateers accidentally encountered, they are detachments of an army. They are also portents.

We were scoffed at long since for "pouring medicines of which we know little into bodies of which we know less". Browne (1954), reporting the moniliasis, remarks: "one of the risks of using antibiotics is that their selective action may disturb the bacterial equilibrium of the gut or lung".

There are parallels in agriculture.

We plough the fields and scatter insecticides and selective weed-killers on the land and we find we have killed birds, bees and flowers who minister in various ways to our health and happiness and with whom we have no quarrel. With a little more knowledge I am sure I could tell you of pests we have unwittingly encouraged. We should study the balance of Nature in field and hedgerow, nose, throat and gut before we seriously disturb it.

Again, we may come to the end of antibiotics. We may run clean out of effective ammunition and *then* how the bacteria and moulds will lord it.

A leader-writer quotes the Mayo Clinic who "wish to emphasize that they do not advocate the use of erythromycin in chronic infections such as osteomyelitis, bacterial endocarditis, &c., because of the strong likelihood of provoking bacterial resistance. They *abhor its indiscriminate use*" (*see Brit. med. J.*, 1954).

"ὁ βίος βραχὺς, ἡ δὲ τέχνη μάκρα" "Life is short but the Art is long."

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Dr. J. D. N. Nabarro: The abuses of antibiotics may be considered under two headings, using them unnecessarily and using them unwisely.

Antibiotics may be regarded as being used unnecessarily when they are given by injection, by mouth, or used as a local application in cases of minor or self-limiting conditions from which a good recovery may be expected without their use. If the antibiotics were completely innocuous drugs with a potentiality only for doing good, the sole objection to their use in minor illnesses would be their cost—admittedly an important consideration in some instances. In fact, however, this is far from the case. There are at least four ways in which the unnecessary use of antibiotics may be harmful to the individual patient, or to the population in general. It may harm the patient by giving rise to undesirable side-effects, it may harm him by interfering with the development of antibodies and it may harm him by sensitizing

him to the antibiotic—so that, at some time in the future when he really does need it, he gets an unpleasant reaction. From the point of view of the population as a whole, the widespread and unnecessary use of antibiotics is most undesirable because it encourages the emergence of resistant strains. Some of these points may be considered in greater detail.

Most doctors have encountered cases in which antibiotics given for minor ailments have given rise to side-effects more troublesome than the original illness. Common examples are, stomatitis following the use of penicillin lozenges, an eczematous reaction produced by a local application of penicillin cream and intractable diarrhœa after a short course of one of the broad-spectrum antibiotics. If these complications occur when the antibiotic is being used for the treatment of a severe illness, they may reasonably be looked upon as part of the price to be paid for recovery. If they follow treatment of a minor ailment, the patient has some justification in claiming that the cure is worse than the disease.

In this country, intramuscular penicillin is looked upon as a form of medication that can be given without fear of untoward side-effects. There is a tendency to give it in borderline cases because it may do some good and cannot do any harm. In contrast to this two recent American views may be quoted. Sheldon Swift (1954) has pointed out that about 10% of outpatients attending a New York hospital are recorded as being sensitive to penicillin, and that anyone who has had a minor reaction to this antibiotic in the past may get a fatal anaphylactic reaction if given an intramuscular injection of it. Barach (1954) regards the dangers of anaphylactic reaction and sudden death following penicillin injections so seriously that he thinks that "perhaps the time has come to limit penicillin by injection to those cases in which exceptionally high blood levels are needed for survival such as subacute bacterial endocarditis". In other cases he would give oral penicillin in coated tablets at a dose of one million units three times a day before meals.

The second danger of using antibiotics unnecessarily—the risk of sensitizing the patient so that when he really does need the drug he gets an unpleasant reaction to it—needs little elaboration. The most troublesome type of sensitization reaction is the eczematous one and this may go on to an exfoliative dermatitis. It usually occurs in patients who have some skin disease and the original sensitization has been produced by local application of an antibiotic ointment or paste. There is a welcome tendency to use for local application antibiotics that are generally regarded as being too toxic for parenteral administration—substances like neomycin and bacitracin.

The most important objection to the use of antibiotics in minor illnesses is the increasing proportion of bacteria found to be resistant after the widespread use of an antibiotic. The staphylococcus is the organism that most easily produces antibiotic resistant strains, and the extent to which this occurs seems to be related to the amount of the antibiotic in general use. This is well brought out in Table I which is derived from data published by Spink (1954) for

TABLE I.—Percentage of staphylococci isolated from patients attending the University of Minnesota clinics resistant to antibiotics. Data derived from: A.M.A., *Arch. intern. Med.*—Spink—Aug. 1954.

Resistant to	1951	Isolated in 1952	1953
Penicillin	63%	57%	63%
Streptomycin	48%	49%	65%
Chlortetracycline	23%	33%	63%
Oxytetracycline	38%	48%	63%
Erythromycin	—	0	18%
Chloramphenicol	25%	3%	1%

the resistance of staphylococci obtained in the years 1951 to 1953 from patients at clinics run by the University of Minnesota. Over this period penicillin resistance was steady at about 60%, streptomycin resistance rose slightly. During the years 1951 and 1952, chlortetracycline and oxytetracycline were being used extensively in the U.S.A. and the percentage of resistant organisms rose from 23% and 38% to 63%. In the case of the more recently introduced erythromycin the percentage rose from nil to nearly 20% in the first year. In this country erythromycin should be very useful for treating illnesses due to strains of staphylococci resistant to other antibiotics but if it is used indiscriminately there is little doubt that the percentage of organisms resistant to it will soon rise. The most interesting feature of this table is the virtual disappearance of chloramphenicol-resistant staphylococci. Reports of aplastic anæmia following this antibiotic were published in America in 1952; subsequently very little of it was used and the incidence of resistant strains decreased remarkably. It appears, therefore, that the emergence of resistant strains is closely related to the extent to which an antibiotic is used. The only way to minimize this change in the bacterial population is to cut down as far as possible the amount of antibiotic used and to reserve it for cases in which it is really needed. If we fail to do this, if we continue to

prescribe antibiotics for minor ailments, we may well produce a situation in which all the patients but none of the organisms are sensitive to them.

Turning to the second form of abuse of the antibiotics—using them unwisely, one is concerned with matters of detail rather than general principles. I should like to draw attention to a few points based either on published reports or on personal experience. It is unwise to give streptomycin to a patient with chest disease of uncertain ætiology or pyrexia of unknown origin. If the condition responds to this antibiotic the physician is often left in a quandary. The underlying cause may well have been tuberculosis, in which case streptomycin with supporting chemotherapy should be continued for from three to six months. If the condition is non-tuberculous such prolonged treatment is unnecessary. Care is also needed when streptomycin is given to patients with acute or chronic renal failure. About three-quarters of an injection of streptomycin is excreted in the urine. If it is given in the usual doses to patients with renal failure, very high blood levels may result. There is one report of fatal encephalopathy having been produced in this way (Hunnicutt *et al.*, 1948).

It is not yet possible to say with any certainty what constitutes the unwise use of chloramphenicol. Repeated or prolonged courses may give rise to aplastic anæmia with a high mortality rate, but the incidence of this dramatic complication remains uncertain. The Council on Pharmacy and Chemistry of the American Medical Association (1954) has advised that the use of chloramphenicol should be confined to cases of typhoid fever and other serious infectious illnesses that cannot be treated with any other antibiotic. Under the latter may be included severe infections due to staphylococci resistant to the remaining antibiotics and *H. influenzæ* meningitis. It is worth noting that many of the reported cases have occurred in patients given repeated courses for recurrent urinary tract infections.

An interesting situation arose when chlortetracycline was first introduced. Nausea and vomiting were described as troublesome complications and in the early reports it was claimed that this could be prevented or reduced by the use of aluminium hydroxide gel (Schoenbach *et al.*, 1948). Shortly afterwards, however, it was shown that the aluminium hydroxide interfered with the absorption of chlortetracycline and that when the two were given together the blood levels were less than when the antibiotic was given alone (Waisbren and Hueckel, 1949). A good way of preventing this nausea and vomiting is to give the chlortetracycline with a glass of milk or yoghourt (Barach, 1954).

There is a tendency in hospitals to try combinations of antibiotics, if one alone fails to control an infection. Although there is excellent evidence that penicillin and streptomycin have a synergistic action the important experimental and clinical evidence of antagonism between the broad-spectrum antibiotics on the one hand and penicillin and streptomycin on the other, is often forgotten. Lepper and Dowling (1951) studied 28 patients with pneumococcal meningitis. All were treated with one mega unit of penicillin two-hourly by intramuscular injection and alternate cases in addition received 0·5 gram chlortetracycline intravenously every six hours. The cases were apparently of comparable severity but whereas only 3 of the 14 treated with penicillin alone died, 11 deaths occurred among the 14 given chlortetracycline in addition. This is a striking confirmation of the previously demonstrated action of chlortetracycline interfering with the bactericidal effect of penicillin (Gunnison *et al.*, 1950).

Some of these are admittedly minor abuses of the antibiotics but they are points that can easily be overlooked. By far the greatest dangers are those of widespread sensitization of patients and the development of resistance on the part of the bacteria.

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Dr. John Fry: The use of antibiotics in general practice presents special problems regarding the indications for their use and the methods of their administration.

There is only one absolute indication for the use of these drugs—namely, infection by sensitive organisms. The problems are the accurate clinical diagnosis of these conditions and the proper assessment of each case to decide whether they are really necessary to help the body's natural defences.

In spite of the introduction of the many new antibiotics *penicillin* is still the safest and most useful in general practice. It should be administered by intramuscular injection, when indicated, except in infants. In this way its use will be more restricted to appropriate cases, its effects will be more reliable and it will be the most economical way of administration. When prescribed, it should be administered by the practitioner himself, for in my opinion any case which needs penicillin also requires daily medical supervision.

There are very few indications in general practice for the newer wide-spectrum antibiotics and in many ways it is a pity that the restrictions regarding their use have recently been lifted. There was a lot to be said for the old system whereby their use was restricted to certain specified conditions. In my own practice over a period of one year (1954–5) antibiotic and chemotherapeutic drugs were prescribed to 350 patients out of the 5,000 at risk, indicating the wide uses of these drugs. Tables I and II show the conditions for which they were necessary and the preparations which were used.

TABLE I.—DISEASES REQUIRING ANTIBIOTICS IN ONE YEAR IN A GENERAL PRACTICE

Skin and subcutaneous infections	113	32%
Eye infections	48	14%
Acute chest infections	47	14%
Acute throat infections	47	14%
Acute otitis media	36	10%
Genito-urinary infections	31	9%
Tuberculosis	8	2%
Others	20	5%
	350	100%

TABLE II.—DRUGS USED

Penicillin		273	78%
I.M.	264		
Oral	9		
Local	—		
Sulphonamides		44	12·5%
Chloramphenicol		29	8·5%
Oral	14		
Local	15		
Chlortetracycline (Aureomycin)		4	1%
Oral	2		
Local	2		

In general practice it is necessary to use *techniques* which are compatible with the rush and tear in this field. Single daily penicillin injections are therefore needed. I have found that high dosage of procaine penicillin (600,000 units) combined with soluble penicillin (200,000 units) (Abbocillin) is satisfactory. Long courses of penicillin, as recommended by many consultants in hospital practice, seem unnecessary in general practice and in the vast majority of cases, including serious conditions such as pneumonia, the infection can be controlled by as few as one daily injection for four days.

The abuse of antibiotics occurs only in connexion with oral therapy and could be limited if penicillin (by the intramuscular injection) or sulphonamides were used in the first instance and if the following points were borne in mind: (i) antibiotics should never be used without first making a definite diagnosis, (ii) if no clinical response is obvious in forty-eight hours—then the case must be carefully reassessed, and (iii) a more complete knowledge of the natural history of the many common infections will show that they will in many instances clear up without the use of these potent drugs.

We must always remember with respect the wonderful natural defences of the human body.

Dr. Horace Joules advocated sulphonamides alone for cases of acute tonsillitis. These resulted from infection by streptococci in over 90% and the response was excellent. No case of acute rheumatism or nephritis had occurred in the past fourteen years among the nursing staff where such treatment had been given.

Pneumonia, in adults, unassociated with an influenzal epidemic, was best treated initially by these drugs as 95% would respond; for boils he preferred intramuscular penicillin 250,000 units b.d. and streptomycin 1·0 gram b.d. for three to four days. If these tended to recur the source was often to be found in the nose when streptomycin inhalations three times daily for one week would usually cut short the tendency.

Dr. B. W. Lacey (Westminster Medical School): I should like to mention three points which appear important enough to be considered as precepts of antibiotic therapy. The first concerns the use of substances such as streptomycin, and probably erythromycin also, to which most bacteria rapidly develop a high level of resistance. It seems reasonable to make it a rule that these should not be given alone, but always with another drug, so that the chances of a resistant mutant appearing are much reduced. And because resistance to streptomycin, and probably erythromycin too, can be developed by some organisms in less than a day it is probably advisable to saturate the patient with the second drug (usually a sulphonamide or penicillin) beforehand. With streptomycin and erythromycin the infected site should be made alkaline if possible before treatment is started. This applies, of course, most to infections of the urinary tract where, for example, alkalinization may increase the activity of streptomycin eightfold or more.

The second is a principle of prophylaxis. I think most people would agree that the dangers of the indiscriminate use of chemoprophylaxis in surgery, or against chest infection, &c., should not lead to a general ban on the use of antibiotics in prophylaxis: the administration of penicillin orally for many years in order to prevent a recrudescence of rheumatic carditis appears entirely justifiable. But as a general rule the drug used in prophylaxis should not be that upon which reliance must be placed if the prophylaxis fails. Professor Garrod and others have drawn attention to the danger of giving penicillin for several days before a tooth extraction to a patient predisposed to subacute bacterial endocarditis. On several occasions this practice has been followed by an endocarditis with a fæcal type of streptococcus, highly resistant to penicillin, which had almost certainly been selectively cultivated in the mouth by the prophylaxis. Probably the best course here is to give one of the tetracyclines not more than twelve hours beforehand.

My third point concerns the use of antibiotics locally. When a substance is known to be highly sensitizing it seems reasonable to make it a rule that only exceptional circumstances can justify its use locally. Although the risk is not inconsiderable with penicillin and sulphonamides, it appears greatest with streptomycin and the use of streptomycin in the nose seems most unwise.

One speaker said that he preferred giving a sulphonamide rather than penicillin to young nurses with streptococcal sore throats. This is a curious choice, for there appear to be three good reasons why, for streptococcal infections in young people, penicillin is preferable and which together form almost a legal obligation to give penicillin rather than a sulphonamide. Firstly, all streptococci playing a part in rheumatic fever are believed to be sensitive to penicillin (and never develop resistance) whereas many, or even most in some environments, are comparatively resistant to sulphonamides. Secondly, the toxicity of effective penicillin therapy is unquestionably much less than that of any sulphonamide. Lastly, there is a delay of eight hours or longer before sulphonamides begin to be effective, whereas penicillin acts very rapidly. But in these infections the object of chemotherapy differs from that in, for example, scrub typhus. With streptococcal infections in young people one wants to abolish the infection entirely, as soon as possible, in order to reduce to a minimum the subsequent development of tissue toxic antibodies, whereas in rickettsial infections some immunity mechanism is desirable to eradicate the infection and immediate therapy may lead to a recrudescence.

Although almost all speakers here agree that penicillin should not be used for treating simple boils, I think they have only mentioned giving X-rays or doing nothing as alternatives. But autogenous vaccine with toxoid offers a fair chance, perhaps four to one, of a lengthy remission or complete cure and, with a six-months history, the unpleasantness of the complaint far outweighs that of the inoculations.

My last point refers to the use of antibiotics in virus diseases. There are only a few human diseases undoubtedly caused by viruses or virus-like microbes which are susceptible to chemotherapy. These are: psittacosis, trachoma, inclusion conjunctivitis or urethritis, and lymphogranuloma venereum. They all belong to one, clearly defined, biological group which taxonomists are beginning to regard as rickettsial. For therapeutic purposes, at least, it seems an advantage to accept this, for it makes possible the waste-saving generalization that no human virus disease is casually treatable at present with any chemical. Extravagant claims by manufacturers of antibiotics might then yield less profit and raise fewer false hopes.

Sir Henry Cohen: We should keep a sense of proportion. The discussion has been over-weighted with the toxic hazards of penicillin, but it should not be forgotten that the sulpha-drugs are relatively more toxic. We must not overlook the blood changes, dermatitis, renal lesions and other toxic complications of their exhibition, and their probable role in such collagen disorders as systemic lupus erythematosus and periarteritis nodosa. Penicillin is still most widely used despite the advent of the newer antibiotics. I have been struck by the fact that penicillin is responsible for 50% of the antibiotic bills in every large hospital in my own region, and I have no reason to doubt that these reflect the general picture. Antibiotics can, of course, be abused, both in treatment and in prophylaxis, and there would appear to be risks associated with the indiscriminate use of penicillin "umbrellas" as pre-operative and pre-parturient measures, which should be more widely appreciated.

The physician should ever remain on the alert to perceive the altered clinical picture produced by antibiotic therapy. For example, the eradication of the infective factor in a renal mycotic aneurysm occurring during the course of a subacute bacterial endocarditis, does not of itself remove the damage to the arterial wall. Consequently, the aneurysm may continue to enlarge and unless tackled surgically may rupture with grave consequences. *Primum non nocere* should remain the guiding maxim in antibiotic therapy.

Section of Medicine

President—Professor Sir HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P.

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"SUMMINGS-UP"

The Chemotherapeutic Treatment of the Reticuloses

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THE reticuloses may first manifest themselves clinically in a variety of ways as by enlargement of the lymphatic glands, spleen and liver, skin lesions, changes affecting the skeletal system, different forms of leukæmia, or by blood changes associated with refractory forms of anæmia. In general these can be considered for therapeutic purposes under the following groups, (*a*) Leukæmia (acute and chronic); (*b*) Hodgkin's disease; (*c*) Other reticuloses (such as follicular lymphoreticulosis or Brill-Symmer's syndrome, lymphoid reticulosis, giant cell reticulosis, reticulum cell reticulosis) and (*d*) Myelomatosis, mycosis fungoides, &c.

Chemotherapeutic Agents

Since I first used tri-(2-chlorethyl)-amine hydrochloride and di-(2-chlorethyl)-methylamine hydrochloride in 1942 for the treatment of leukæmia and Hodgkin's disease very many simple and complex chemical substances have been made and tried in the treatment of the reticuloses and of malignant disease with variable and usually disappointing results; some of these have already been discussed recently at a meeting of this Section (Wilkinson, 1953). Those substances of any value in the treatment of the reticuloses fall broadly into three main groups (Wilkinson, 1955):

(*a*) Substances having specific nucleotoxic action—arresting mitosis, inhibiting cellular enzyme reactions and thus interfering with leucopoieses in the marrow, such as the 2-chloralkylamines (nitrogen mustards), urethane, Myleran, colchicine and desacetyl-methylcolchicine.

(*b*) Substances that act as metabolic antagonists to specific substances essential for cell growth and among these are folic acid antagonists (such as Aminopterin and amethopterin) and 6-mercaptopurine.

(*c*) The hormones—cortisone and adrenocorticotrophin.

The ideal therapeutic agent for these diseases must be capable of correcting the marrow dyscrasias to permit of a return to normal blood cell formation, inhibition of abnormal pathological processes taking place in other tissues, such as lymph glands, spleen, skin, skeleton, without causing damage to normal tissues or producing other lesions such as aplastic anæmia, thrombocytopenic purpura, agranulocytosis, &c.

Nitrogen Mustards (2-*chloralkylamines*)

The first employed by me and still the most effective are tri-(2-chlorethyl)-amine and di-(2-chlorethyl)-methylamine given intravenously in the form of their very soluble hydro-chlorides; the former is the most effective as the latter tends occasionally to cause some local venous thrombosis. Their local and general effects have been fully described previously but the most striking changes are those seen in the blood and marrow and their extremely rapid and effective ability to reduce in a few days even the most marked leucocytosis and gross glandular and splenic enlargement (*see* Wilkinson and Fletcher, 1947; Wilkinson, 1953). This is particularly valuable where there is widespread involvement throughout the body and not localized to one group of glands. Hence, these substances are of the greatest value in the treatment of chronic leukæmias and especially generalized or widespread Hodgkin's disease. The white blood cells of the leukæmic patient as well as the normal person are very sensitive to the nitrogen mustards so that I rarely give a dose if the leucocyte count is below 15,000 per c.mm. On the other hand, in Hodgkin's disease and other similar reticuloses the leucocytes do not appear to be anything like so sensitive and therefore nitrogen mustards can be given to them with white blood cells as low as 4,000 c.mm. The nitrogen mustards are effective at any stage of the disease but it is desirable to use them without the complication of prior X-ray therapy which so frequently leads to marrow damage and the production of a severe refractory or aplastic anæmia.

The main therapeutic advantages of the 2-chloralkylamines are:

(1) With a correct technique they are very safe to use and then do not produce other hæmatological complications.

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(2) Easy to control with proper dosage and adequate hæmatological supervision.

(3) Further courses can be repeated as required and usually have equally good effects.

(4) Longer intervals, between treatment, of symptomless improvement.

(5) They are easily given intravenously in out-patient clinics thus reducing very considerably the need for hospitalization and the time required for treatment—a considerable economic advantage as no special equipment is needed.

(6) They produce the most rapid relief of general systemic symptoms, and usually prompt reduction in the size of enlarged glands, liver, spleen, and often bone metastases.

(7) Marked leucocytosis in chronic myeloid and lymphatic leukæmias is rapidly diminished to the level required.

(8) With the above improvements the patient rapidly gains weight and feels much better.

(9) The effects may last for several months or years in some patients before a further course is required.

The disadvantages are:

(1) A good intravenous technique is essential.

(2) Nausea and occasionally severe vomiting may occur in 20% and 2% of patients respectively.

(3) Inadequate hæmatological control or overdosage may cause aplasia, or leucopenia.

R.48 (β-*naphthyl-di-(2-chlorethyl)-amine*)

R.48 is one of a series of substances produced by Haddow and colleagues (1948) and can be given orally in doses of 50–800 mg. (most usually 100–300 mg.) daily. Although relatively non-toxic and mild it has proved disappointing in most cases but I have found it of value in some patients with Hodgkin's disease or chronic lymphatic leukæmia having very poor veins unsuitable for intravenous therapy (Gardikas and Wilkinson, 1951; Wilkinson, 1953); Ramioul (1954) has also found it of value in Hodgkin's disease given orally or intramuscularly.

Urethane (*$NH_2.CO.OC_2H_5$*)

Urethane in doses of 1–3 grams orally has a place in treatment although inferior to nitrogen mustards, but requires careful control, as it tends suddenly and without much prior warning to produce aplastic anæmia or leucopenia (*see* Wilkinson, 1953).

Myleran (1:4-*dimethanesulphonyloxybutane*)

Myleran, described by Haddow and Timmis (1953) and Galton (1953), has certainly proved of great value in treatment of chronic myeloid leukæmia in doses of 1–4 mg. daily or less frequently, with adequate hæmatological control. We found that in a group of 20 cases good results were obtained in 17 cases. Ultimately patients may fail to respond to this treatment or develop aplastic anæmia or thrombocytopenia or severe anæmia necessitating discontinuance of treatment. Nevertheless, it has a valuable place in therapy.

6-*Mercaptopurine*

6-Mercaptopurine was introduced by Burchenal and others (1953) for the treatment of chronic myeloid leukæmia and acute leukæmia but it had no value in chronic lymphocytic leukæmia, or Hodgkin's disease. In a way it has not lived up to its expectations and in my experience it seems to have had the most beneficial effects in chronic myeloid leukæmia in its acute myeloblastic phase especially in those becoming resistant to Myleran and other agents; we have not had any striking results in acute leukæmia, but Burchenal says it may take 3 to 8 weeks to see any results if the patient has minimal hæmorrhagic manifestations and is likely to survive that necessary period for treatment.

Desacetyl-methylcolchicine

Following the observations that colchicine could have an effect on leukæmic processes in spite of its toxicity a substituted derivative desacetyl-methylcolchicine (Colcemid) has been prepared and a few cases were reported by Moeschlin and others (1954). In a group of cases that Leonard and I have investigated, there is no doubt it is of value in the treatment of chronic myeloid leukæmia. It is of no value in chronic lymphatic leukæmia and proved of little use in acute leukæmia. It certainly provides a rapid fall in the white cell count, and marked reduction in the size of the spleen without impairing the red cell and platelet counts (Leonard and Wilkinson, 1955).

Triethylene melamine (2.4.6.-*triethyleneimino-s-triazine*; *T.E.M.*)

This is a powerful and quite toxic substance that has been used parenterally in doses of 0·15–0·18 mg./kg. bodyweight but its effects are somewhat unpredictable since individual tolerance varies so much and marrow aplasia or leucopenia can readily occur in a high proportion of cases as has been noted by most users of it.

Its activity seems to be associated with its ethyleneimino groups—which resemble the ethyleneimonium transformations that occur with the nitrogen mustards (Wilkinson, 1955).

Many other substances have been tried such as TEPA (NN′N″triethylenephosphoramide), DEPA (NN′diethylene phosphoramide) and more recently THIOTEPA (triethylenethiophosphoramide) which can be given intramuscularly, with variable but encouraging results.

Folic Acid Antagonists

The only ones of particular interest and value in this group have been Aminopterin (4-aminopteroylglutamic acid) and amethopterin (4-amino-N^{10}-methylpteroylglutamic acid). They have been used most effectively both orally and parenterally in the treatment of acute leukæmias (Farber *et al.*, 1948; Farber, 1949) and reticuloses, and my own results have been described fully elsewhere (Wilkinson, 1948, 1953; Wilkinson and Gardikas, 1951).

They appear to act as antimetabolites which, in the specific enzyme system concerned, prevent folic acid from stimulating abnormal leucocyte formation in the marrow: The most effective results have been noted in children with acute leukæmias.

Cortisone and ACTH

The mode of action of these hormones in the treatment of the leukæmias and reticuloses is unknown—nevertheless, they play an important, though temporary, role in the successful relief for a time of acute leukæmias, especially in children. According to different authors 30–90% of children with acute leukæmia show remissions that may last for up to twelve months. Subsequent treatment after relapses is not so effective. Nevertheless, a smaller group of patients do get longer and complete remission—my longest case, a girl of 7 years, has now survived three and three-quarter years, is clinically normal and has still got a completely normal blood count and bone-marrow. These hormones are quite definitely the best treatment for acute leukæmias at the present time but have little or no value at all with the other reticuloses.

Results

In discussing the treatment of the various reticuloses with chemotherapeutic agents I shall consider them in the light of the results in my own series of over 700 patients treated since 1942, although the majority of necessity date from 1946.

Since it is quite well known that many mild cases of Hodgkin's disease and chronic lymphatic leukæmia, especially in older patients, are quite benign and often do not require treatment over many years, if at all, all my treated patients in this series were moderately severe or very severe cases, some having failed to respond adequately to previous radiotherapy. The mild types of cases were not treated at all unless they later developed more severe conditions necessitating this.

Hodgkin's disease (Tables I, II, Fig. 1)

In Table I it will be seen that 80 patients treated with nitrogen mustards intravenously

TABLE I.—HODGKIN'S DISEASE

Agents used	No. of cases	Total dosage	Regression of Spleno-megaly	Regression of Lympha-denopathy	Survivals	Therapeutic effects
Tri-(2-chlorethyl)-amine Di-(2-chlorethyl)-methylamine	80	6–174 mg.	*Complete* (1–4 weeks) 76%	83%	16 weeks–11 years	Very good
			Partial 16%	9%		Good
			None 8%	8%		—
β-naphthyl-di-(2-chlorethyl)-amine (R.48)	20	2–94·7 grams	*Complete* (3–21 weeks) 30%		4 well after 2½–5 years 2 died–other causes 1–2 years	Good
			Partial 40%			
			None 30%			
Urethane	6	30–50 grams	None		1–5 months	None
Cortisone	7	700–2,000 mg.	None		—	None
ACTH	6	500–2,000 units	None		—	None

showed very good therapeutic results with survivals up to eleven years (these agents in general have only been used during the last ten years, with a few patients treated before that period) on total doses of 6–174 mg.—*complete* regression of spleen and glands being noted in 76% and 83% respectively, only 8% failing to do so. Moderate results were
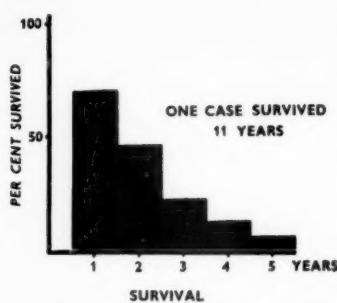
FIG. 1.—Hodgkin's disease: 58 cases treated with tri-(2-chlorethyl)-amine hydrochloride.

obtained with R.48 in 20 patients with total dosages of 2–95 grams; of these 30% (6 cases) were completely relieved in three to twenty one weeks, 4 being still alive after two and a half, three, three, and five and a half years respectively; 1 died of auricular fibrillation (two years) and 1 of cerebral hæmorrhage ten months later. Urethane (6 cases), cortisone (7 cases) and ACTH (6 cases) had no beneficial effects.

Of 58 severe patients treated for at least twelve months prior to January 1953 the survivals are shown in Fig. 1.

Of other reticuloses only intravenous tri-(2-chlorethyl)-amine hydrochloride given to 20 patients (12–40 mg.) produced any beneficial results up to two years as will be seen by referring to Table II.

TABLE II.—RETICULOSES

Follicular Lymphoblastoma, Myeloid Reticulosis, Acute Reticulosis, Reticulum cell Reticulosis

Therapy	Total dosage	No. of cases	Therapeutic effects	Survival (months)
Tri-(2-chlorethyl)-amine	12–40 mg.	20	Temporary and partial	1–24
R.48	1–36 grams	5	None—4	1–13
			Partial response—1	
Urethane	30–100 grams	6	None	1–6
Cortisone	1–2·6 grams	8	None or very slight	½–15
ACTH	1,400–3,000 units	6	None or very slight	½–15

Chronic Leukæmias

As already mentioned above, the mild elderly patient with chronic lymphatic leukæmia usually requires little or no treatment (*see* Wilkinson, 1953, 1955).

The most rapid and effective therapy is by intravenous nitrogen mustard which will reduce the high leucocyte count in the course of a few days, cause rapid reduction in size of spleen, liver and glands, and is undoubtedly the quickest method of relieving mechanical pressure symptoms due to enlarged organs and glands.

Of 126 patients with chronic myeloid and lymphatic leukæmias there were 70 myeloid cases with splenomegaly who showed complete regression in 46% and partial improvement in a further 48%, while 31% of the lymphatic cases likewise showed complete regression and a further 60% partial reduction in size of the spleen. These reductions in the spleno-megaly were accompanied by complete clinical improvement and only 5·7 and 9·0% of the myeloid and lymphatic patients respectively showed no improvement.

Similar profound improvements were noted in fatigability, anorexia, fever, sweating and loss of weight (*see* Table I, Wilkinson, 1953).

In these patients with chronic leukæmia the duration of remissions between separate courses of treatment comprising 1–4 injections of 5–6 mg. each were 2 patients for more than two years, 11 (thirteen to twenty-four weeks), 14 (seven to twelve months), 31 (four to six months), and 59 (one to three months), i.e. 21 and 46% of patients did not require further treatment for at least three and six months respectively.

In a comparison with other similar series receiving treatment by irradiation the survival figures from commencement of treatment compare very well indeed as will be seen in Table III.

TABLE III.—CHRONIC LEUKÆMIA: SURVIVAL SINCE START OF TREATMENT

Reference	No.	Treatment	Months
Myeloid			
Hoffman and Craver (1931) ..	71	Irradiation	31
Vogt (1949)	86	Irradiation	19
Wintrobe and Hasenbush (1939)	23	Irradiation	20*
Wilkinson (this series) (1953) ..	80	Nitrogen mustard	29 (2–58)
Lymphatic			
Vogt (1949)	65	Irradiation	19
Wilkinson (this series) (1953) ..	51	Nitrogen mustard	26 (1–36)

* Since diagnosis established.

30 patients with chronic myeloid leukæmia received full courses of Myleran therapy and of these the survivals to date are as follows:

Duration of treatment (months)	1–6	7–12	13–18	19–24	>24
Alive	4	2	4	1	3
Dead	8	3	4	1	0

The value of 6-mercaptopurine in the treatment of chronic myeloid leukæmia is still under investigation but it seems to be quite hopeful: splenomegaly rapidly diminishes, the high white cell count is reduced quite promptly, but less rapidly than with the nitrogen mustards, while the hæmoglobin and red cell count increase. Thus in one patient who received 200 mg. daily for eighteen days and then continued on a maintenance dose of 50 mg. the white cell count was reduced from 272,000 to 31,000, the hæmoglobin rose from 54% to 94%, the spleen became impalpable and she was well seven months later.

A new series of 7 previously untreated patients with chronic myeloid leukæmia were given desacetyl-methylcolchicine (Colcemid) (initially 5–10 mg. and maintenance 2–5 mg. daily) orally with most encouraging results (Table IV), and it will be noticed that the splenc-

TABLE IV.—CHRONIC MYELOID LEUKÆMIA TREATED WITH DESACETYL-METHYLCOLCHICINE (COLCEMID)

Case	Initial (i) White cells/c.mm. (ii) Hæmoglobin	After treatment (i) White cells/c.mm. (ii) Hæmoglobin	Number of days of treatment	Total dosage mg.	Maximum daily dosage mg.	Main- tenance dose mg.	Effects on splenomegaly (cm. below costal margin)
F.6	136,000 58%	4,100 71%	21	76	10	3	13 → 2
M.72	116,000 60%	3,900 69%	14	63	5	4	16 → 0
F.62	180,000 50%	5,500 64%	36	74	10	5	11 → 4
F.44	427,000 62%	26,000 82%	43	302	10	5	13 → 2
M.44	299,000 55%	13,050 70%	42	126	10	—	12 → 4
M.59	57,000 70%	6,950 73%	14	42	5	4	10 →10
M.34	104,000 98%	65,000 90%	35	120	10	—	11 → 9

megaly was markedly reduced in 5 patients and partially in 1 other, only 1 failing to improve in this respect, although all of them showed marked lowering of the high white cell count and an increase in the red cell count and hæmoglobin with great improvement in their general clinical conditions.

Acute Leukæmias

It has been well established now that almost without exception any form of treatment effective for chronic leukæmia (whether chemotherapy or radiotherapy) is quite ineffective for the relief of acute leukæmias.

However, I have demonstrated (Table I in Gardikas and Wilkinson, 1952; Wilkinson, 1953) that when the white cell count is much increased, as may occur at times in acute leukæmia, one intravenous injection of 6 mg. of tri-(2-chlorethyl)-amine hydrochloride may be quite adequate to reduce the count to normal levels, thus permitting the appropriate therapy to be instituted for the acute phase.

A series of 43 patients with acute leukæmia were given Aminopterin by Wilkinson (1948, 1951) and Wilkinson and Gardikas (1951) who found that 10 patients (23%) (5 myeloblastic, 3 lymphatic and 2 monocytic leukæmia) had complete (2) or partial (8) remissions (*see* Table VII Wilkinson, 1953).

After treatment with cortisone or ACTH given to a group of 76 patients with acute leukæmias of different types, 52 failed to show any clinical or hæmatological responses. Of the remainder, 17 (7 myeloblastic and 10 lymphatic) had partial remissions while 7 (4 myeloblastic and 3 lymphatic) responded completely, i.e. there was clinical and hæmatological improvement in 31% (24 cases) of the whole series (*see* Tables IX and X, Wilkinson, 1953; Tables VIII, IX, X, Wilkinson, 1955). As mentioned above, the longest surviving patient with acute lymphatic leukæmia in this group, and one of the first to be treated, is still alive after three and three-quarter years with a normal blood count, bone-marrow and clinical condition. Other patients have survived for lesser periods of twelve to twenty-four months.

Myelomatosis

The treatment of this condition has always been disappointing, the most helpful agents having been urethane, nitrogen mustards, ACTH (cortisone) and the various substituted stilbamidines. In my experience by far the best results have been obtained by the use of urethane in doses of 1–3 grams daily orally, and my results are summarized in Table V

TABLE V.—MYELOMATOSIS

Treatment	Total dosage	No. cases	Therapeutic effects	Survival
Urethane	4–1,635 grams	19	Slowing of disease, relief of pain, temporary partial healing bone tissues in some	7 alive: 2½–18 months 7 lived 0–6 months 1 lived 7 months 3 lived 13–18 months 1 lived 42 months
Tri-(2-chlorethyl)-amine hydrochloride ..	12–30 mg.	2	Nil	—
ACTH	1,400–2,000 units	3	Nil	3–4 weeks
Stilbamidines ..	Various	10	Nil	—

showing that in 19 patients there was slowing of the disease process, prolongation of life relief of pain and, quite often, temporary healing of the bone lesions.

Summary

The chemotherapeutic treatment of the reticuloses is usually an easily controlled, economical and efficient method of dealing with them, particularly where the condition is generalized, severe or in an acute phase; these chemical agents offer the quickest and most effective therapy in these patients and also when there are severe mechanical pressure symptoms or extreme leucocytosis.

For Hodgkin's disease the best and most effective therapy is with tri-(2-chlorethyl)-amine hydrochloride (Trillekamin) intravenously, but in some patients T.E.M. or even R.48 may be of value.

For the other reticuloses such as Brill-Symmers syndrome, follicular lymphoblastoma, myeloid reticulosis, acute reticulosis and reticulum cell reticulosis, the nitrogen mustards and sometimes splenectomy seem to be the best therapy for a very difficult group of conditions.

For the leukæmias there is no doubt that the intravenous nitrogen mustards give the most prompt, effective and long-standing results with both chronic myeloid and chronic lymphatic forms; combined or prior radiotherapy is very undesirable. Good results are also obtained in myeloid leukæmias using Myleran, desacetyl-methylcolchicine (Colcemid), 6-mercapto-purine and urethane orally. In some cases of chronic lymphatic leukæmia, T.E.M. and R.48 orally, or THIOTEPA intramuscularly, have also been of great value.

The acute leukæmias of all types have shown the best results after treatment with Aminop-terin (or amethopterin), or cortisone orally or ACTH intramuscularly or intravenously

Urethane is undoubtedly the best treatment for myelomatosis.

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Radiotherapy versus Chemotherapy in the Treatment of Reticuloses

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THE four main groups of reticulosis are: (*a*) Hodgkin's disease; (*b*) Lymphosarcoma; (*c*) Reticulum cell sarcoma; (*d*) Giant follicular lymphoblastoma.

I will avoid as far as possible discussion of the leukæmias. The material from which my views have been derived consists of cases treated at the Middlesex Hospital from 1930 to 1952.

We have studied 605 unselected cases, of which 245 were Hodgkin's disease, 186 were lymphosarcoma, 51 were reticulum cell sarcoma, 16 were giant follicular lymphoblastoma.

In addition there were a further 107 cases in which histological proof was lacking or which, by reason of their atypical microscopical appearance, did not fall clearly into these four well-differentiated groups.

Radiotherapy has played a prominent part in the treatment of this whole series of cases and it does not therefore provide material with adequate controls for a true scientific assessment of the value of radiotherapy as opposed to chemotherapy. Chemotherapy, mainly in the form of nitrogen mustard, was used only in the last five to six years of the twenty-two-year period during which the cases were treated and even then it was used, as the primary method of treatment, only in cases where the disease had generalized manifestations and in no cases where the disease was apparently localized to a single primary focus or a single group of lymph nodes.

I should like to make clear at the outset that whatever main method of treatment is employed it must be accompanied constantly by general supportive treatment. Blood transfusion is frequently necessary and skilled nursing is essential. I do not consider that radiotherapy and chemotherapy are competitive methods of treatment in these groups of diseases but rather that they both have a valuable place and that it is important to decide in what circumstances the one or the other, or both, should be used.

With these reservations I consider that radiotherapy should be used as the primary method of treatment in all cases where the disease is apparently localized to a single primary focus or to one group of lymph nodes.

In those cases where the patient presents with involvement of nodes in several regions, e.g. both sides of the neck, the axillæ, and the mediastinum, radiotherapy should still be used unless there is evidence of more generalized disease with marked constitutional symptoms.

In almost all the cases in these groups of reticulosis the local lesions are initially markedly radiosensitive and disappear with moderate dosage without the production of severe reactions. After a variable time, recurrence may appear either in the same or in other sites, but can be made to disappear in the same way. Each succeeding relapse tends to be less sensitive to radiation. It may be necessary to increase the dose and even then resolution may be less complete. As the disease becomes generalized it may become unresponsive to radiotherapy. It may then be impossible to treat the extensive involvement without causing damage rather than improvement to the patient's general health.

Chemotherapy, by the use of various cytotoxic substances, particularly the nitrogen mustards, is also effective in causing regression of such local lesions, but those compounds which are effective are also generally toxic and may cause general reactions with nausea, vomiting and depression of the white cell count. By their administration tumours can be made to disappear and infiltrations to regress, but I consider that, with rare exceptions, resolution is less complete than with radiotherapy and the period of remission is usually of shorter duration. Nitrogen mustard and allied compounds have a definite place of value in the later stages when the disease has become generalized; at this stage radiotherapy would involve the treatment of large volumes of tissue and the lesions in many instances have ceased to respond to irradiation. Chemotherapy is also of value in those cases presenting initially with evidence of generalized disease, unexplained pyrexia, pruritus, night sweats, perhaps with splenic enlargement and multiple lymph-node involvement.

Many of these patients eventually die with evidence of generalized marrow failure, perhaps through infiltration by tumour cells but frequently from an aplasia the causation of which may be in part due to repeated treatment by radiation or by cytotoxic poisons. I consider that it is advisable to avoid as long as possible those methods of treatment which have a generalized depressing effect on the bone-marrow and that chemotherapy should not be used for the treatment of localized disease when a more local method of treatment is effective.

Owing to its greater flexibility in technique, X-ray therapy is the usual method of radiotherapy which is used in the treatment of these diseases, though teleradium and moulded gamma-ray applicators may sometimes be of value for localized deposits. The usual

quality of X-rays is a beam generated in the 200 to 250 kilovolt range with a half-value layer of about 2 mm. copper. There are various techniques by which it may be given:

(1) It may be used as a localized irradiation limited to the enlarged glandular masses. If one group of nodes only is involved then that only would be treated. If there are multiple sites of involvement, e.g. both axillæ and mediastinum, the treatment would be localized to each of these areas.

(2) In addition to local treatment of involved nodes, so-called prophylactic irradiation of the nearest lymphatic drainage areas has been used. As described by the Toronto school this technique is reported to have caused a definite improvement in results.

(3) X-ray therapy can be given as a regional treatment to include not only the affected organ or group of nodes, but also the surrounding tissues and the neighbouring apparently unaffected node groups. An example of this would be the treatment of the whole abdomen when mesenteric glands are involved. Levitt has described the details of his X-ray bath technique—there may a thoracic bath, an abdominal bath or a total trunk bath.

Consideration of the 245 cases of Hodgkin's disease in our series will best exemplify the principles which I have suggested.

There was a five-year survival of 30% from the whole group. My colleagues A. M. Jelliffe and A. D. Thomson are at present engaged in making a more detailed study of these cases. They have found that among the patients who, following radiotherapy, have survived more than five years without developing any sign of recurrence, there were some who had only one group of nodes involved at the time of treatment, but there were others who had more than one group of nodes involved. Although the prognosis becomes much worse when deeper glands are involved, there are some cases who have had prolonged remission as long as ten years after irradiation of enlarged mediastinal glands.

Diffuse lung infiltration usually occurs only in the later stages of the disease and does not respond well to irradiation. Localized masses in the lung also do not respond well.

Skin involvement with nodular lesions responds rapidly to irradiation. Generalized pruritus which may occur, particularly when intra-abdominal glands are involved, is variable in response. It may be severe and intractable and may be an indication for chemotherapy.

Bone involvement occurs probably in as much as 15 to 20% of cases. Both osteoblastic and osteoclastic types of involvement occur and both may be present in the same patient and even in the same bone. Pain can be relieved by radiotherapy in the majority of cases. Extradural deposits with or without involvement of vertebræ may call for urgent decompression and then can be controlled by localized irradiation.

There is a considerable variation in the views of radiotherapists as to the level of dosage that should be given. It is taught by many that the dose should be sufficient only to cause clinical disappearance of deposits, a dose of 1,200 to 1,500 r in twelve to fourteen days. This can be achieved with only a mild erythema and the skin remains relatively undamaged. This treatment can be repeated when local recurrence occurs, as it frequently will do. I believe that higher dosage has a place in those cases where involvement is limited clinically to one or two adjacent groups of nodes. In such cases we give a dose of 3,000 to 4,000 r incident over three to four weeks. It appears that when this type of dosage has been used in early lesions we have obtained our longest survivors. Local recurrence is rare in the areas so treated, although there may be recurrence in the same area at a later date when the disease becomes generalized. This method of treatment is comparable to surgical removal and appears to be as effective.

Of 8 patients who survived more than five years without any recurrence, 6 had doses of 3,000 r and over. Of 16 patients whose first recurrence was in the area previously treated, in only 3 was the dose up to 3,000 r and in none was it above this figure.

Although the five-year survival rate of the whole group is 30%, for the years 1937 to 1947 after this more intensive treatment was started, the five-year survival rate was 36%.

When there are several areas involved high dosage of this order cannot be used and when regional or bath treatment is used with a high integral or total body dose the dose level is much lower. I have not personally had any striking success with the bath method of treatment advocated by Levitt, and for the reasons which I have given prefer to keep to local irradiation as long as possible and then to use chemotherapy when the disease becomes generalized.

There were 186 cases of lymphosarcoma with a five-year survival rate of 15%. 15% of them came with primary lesions in a mucosal surface, the tonsil, nasopharynx or in the gut wall. Glands in the mediastinum or abdomen may progress rapidly and cause pressure symptoms such as vena caval or tracheal obstruction.

Some of our cases of lymphosarcoma have progressed into lymphatic leukæmia. Some have had a leukæmoid blood picture when first seen. Some cases of lymphosarcoma have developed from giant follicular lymphoblastoma. We have not yet divided up our cases of lymphocytic and lymphoblastic lymphosarcoma, but the lymphoblastic ones appear to have

a more rapid course and worse prognosis.   We consider that localized lesions need localized high dosage of radiation.   There is then some chance of cure which may perhaps even be a lasting one.   The most favourable types are those with primary lesions in the tonsil, tongue and nasopharynx.   They are most appropriately dealt with by localized irradiation which includes the immediate lymphatic drainage areas.

The majority of cases of lymphosarcoma are very radiosensitive but some do not respond and in particular some cases of bone involvement have been found to be resistant.

Radiotherapy is of the greatest value as a palliative in some cases to obtain rapid relief of pressure symptoms.

We have used nitrogen mustard and other cytotoxic compounds with symptomatic improvement in cases with generalized disease.

Reticulum cell sarcoma has the worst prognosis of all.

20% of our cases had local mucosal lesions in the mouth or pharynx which appeared as a sloughing ulcer or hypertrophic sloughing mass.   It may occur primarily in the bowel wall or in mesenteric glands.   16% presented as acute abdomen.

There may be skin lesions which may be nodular and localized or may be generalized with exfoliative dermatitis.   Bone involvement may occur at any stage.   They are the most rapid in their development and it may be possible to notice even a daily increase in size.

I consider that these cases should be treated on the same lines as I have suggested for lymphosarcoma.   The majority are extremely radiosensitive but some do not respond to even high dosage.

My experience of giant follicular lymphoblastoma is limited to 26 cases: to the 16 cases referred to a further 10 have now been added.   They have presented in almost all cases as a local glandular enlargement which may be a single node and may be large and conspicuous. They tend to progress with involvement of mediastinal and abdominal glands with a tendency to serous effusions.

All our cases have been markedly radiosensitive and they have been relatively benign over a number of years.   Generalization does not appear to give the same bad prognosis as in the other types of reticuloses which I have discussed.   They have not appeared to become more radioresistant if different groups of nodes become involved but some have changed into lymphosarcoma and some have developed a leukæmoid blood picture.

Summary

I have suggested that in these conditions radiotherapy is indicated for localized disease and that chemotherapy should be reserved for generalized manifestations.

In Hodgkin's disease and in giant follicular lymphoblastoma radiotherapy will cause longer and more complete remission.   In localized lymphosarcoma and reticulum cell sarcoma it gives a chance of cure.

For palliative purposes radiotherapy is usually more rapid and more certain in securing regression of a local mass.

Radiotherapy if used as a localized treatment, even if applied to multiple regions, is less likely to cause generalized damage and exhaustion of bone-marrow.

Both these methods have a valuable place and must be used in conjunction with one another.

The Management of Advanced Cancer

By Sir STANFORD CADE, K.B.E., C.B., F.R.C.S., F.R.C.O.G., M.R.C.P.

MANAGEMENT of advanced cancer is in many ways a greater problem than treatment of any given case.   It includes the day-to-day supervision by the general practitioner as well as the highly specialized methods of treatment often needed for the control of pain and the maintenance of life.

Management varies from patient to patient and depends on the nature of the tumour, the site and distribution of lesions, the functional disabilities and the general effects, such as wasting, anæmia and fever.

The main object is the preservation of life with the minimum of symptoms and should result in objective and subjective alleviation.

Advanced cancer implies in all cases extension of disease beyond its site of origin to adjoining tissues and organs and always results in the end in a multiplicity of symptoms due to the metastatic spread.   It presents an ever-varying clinical picture; a constant, although often slow, change of emphasis from one disability to another.   Thus the management of any given patient often needs the services of different specialties and a different approach in the progressive stages of the disease.   The available methods of treatment include surgery, radiotherapy, chemotherapy, hormonal control, symptomatic relief by drugs and a combination of any of these therapeutic measures.

Surgery of Advanced Cancer

In recent years many types of cancer have passed from the control of excisional surgery into the domain of other specialties. It is now recognized by many surgeons that even in common sites such as the breast, the uterus and the lung, the greatest benefits of excision are mainly, if not solely, in the early stages of the disease. Nevertheless, the paradoxical approach that major surgical ablations are only worth while in the earliest stages of the disease, is only true when complete and prolonged control of the disease can be reasonably anticipated. Thus the field of surgery has narrowed where the "curable" case is considered. The very great advances in surgical technique rendered possible by revolutionary developments in anæsthesia, control of infection, blood-loss replacement and better understanding of the chemical needs of the body, have even more paradoxically widened the field of usefulness of surgery in some very advanced cases where previously surgery had nothing to offer.

Outstanding examples of surgical management of advanced cancer are the palliative resection of the œsophagus, multivisceral resections of the abdominal or pelvic viscera. Of these, pelvic viscerectomy is a good example of the application of operative methods to the so-called inoperable case. This procedure which entails the removal of all pelvic viscera, rectum, uterus, bladder, with or without the perineum and vulva, the establishment of a colostomy and a permanent urinary fistula is abundantly justified in a group of cases of advanced and extensive local disease but free from metastatic visceral spread. The justification of this procedure is the vastly increased comfort and a return to a near-normal life. It is chiefly indicated in the presence of vaginal-recto-vesical fistula with loss of control of the bowel and bladder and in the presence of uncontrollable discharge from what can best be described as a cloaca.

The appreciation that cancer of the breast and of the prostate are often not autonomous tumours but hormone-dependent has led to the remote control of disseminated mammary and ovarian cancer by gonadectomy, adrenalectomy or hypophysectomy. Gonadectomy is a simple, safe and minor procedure. In cancer of the prostate it presents many advantages over biochemical castration. It is speedy, simple, effective and devoid of the unpleasant side-effects associated with œstrogen administration. In breast cancer it is effective for limited periods, varying from a few months to two or three years. Adrenalectomy has been rendered possible by the availability of cortisone and in the hormone-dependent cancers of the breast and prostate it is a valuable method in the control of disseminated cancer. Such cases with extensive skeletal or visceral disease, previously uncontrollable by treatment, can now, in a proportion of cases, be relieved of pain and disability and restored, nearly miraculously, to a tolerable and often symptomless existence.

Neurosurgical control of pain, by local section of nerves, cordotomy and leucotomy has a useful place in the management of severe and often uncontrollable pain. Its value is limited to a small group of patients but often renders the terminal stages reasonably comfortable.

Radiotherapy in Advanced Cancer

A wide group of tumours in an advanced stage can be temporarily controlled by a variety of radiotherapeutic measures. Thus it is becoming more widely known that in Stage III cancer of the breast, radiotherapy offers much more than surgery. The rapidly growing, highly malignant, mammary cancer, often present only a few weeks or at the most a few months but already invading the lymph nodes and the lymph vessels, is seldom improved and more often than not made worse by attempts at surgical removal. Such cases can be controlled by radiotherapy sometimes for many years. As the majority of cases of breast cancer still present themselves for treatment in the later stages, radiotherapy is of value to a greater number of patients than surgery. The methods of treatment have altered and the availability of megavolt apparatus, from two million volts upwards, renders it possible to deliver to the tumour a very high dose of radiation with the minimum of damage to the normal tissues and often without any skin changes. The rapid treatment with conventional X-rays spread over three to four weeks is being replaced by a more prolonged overall treatment of two to three months. Technical developments, such as rotation therapy as well as the more powerful apparatus, including the 2 million electron volt generator, the 4 million linear accelerator and the 2,000 curie cobalt units now in clinical use, have rendered radiotherapy a more flexible method of treatment with a wider application, more effective and yet safer and less distressing to the patient.

Other groups of malignant tumours, such as Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and chronic leukæmias in early stages must be looked on as disseminated, generalized malignant processes even in the early stages. In the natural course of this group of neoplasms, only the early stages can be usefully treated by radiotherapy.

Localized metastatic skeletal deposits can be palliated by radiotherapy and relief from bone pain, healing of pathological fractures and recalcification of osteolytic lesions obtained

Isotopes.—Artificial radioactive substances are replacing X-rays and radium as cobalt and cæsium become available. The use of isotopes by injection or by mouth remains limited to a few types of lesions. The most commonly used isotopes are those of iodine, in the treatment of metastases from thyroid carcinoma, radioactive gold, by injection into the pleural or peritoneal cavities in some cases of malignant pleural effusion or ascites and radioactive phosphorus, in the management of polycythæmia and in a few and terminal cases of lymphosarcoma.

Chemotherapy in Advanced Cancer

The value of cytotoxic agents in the management of advanced stages in the reticuloses and chronic leukæmias is now well established. Nitrogen mustard is of great palliative value in the late and apparently terminal stages of Hodgkin's disease. Remissions are obtained even when the liver and spleen are grossly enlarged, in the presence of continued or intermittent fever and when widespread lymph-node enlargement no longer responds to radiotherapy. Oral nitrogen mustard produced by Haddow has given encouraging results as maintenance therapy following a course of injections of nitrogen mustard. The oral substance has also proved of value in multiple myeloma either alone or in combination with œstrogens and has a retarding effect on disseminated malignant melanoma. Triethylene melamine (T.E.M.) has proved of temporary value in lymphosarcoma and in some cases of chronic lymphatic leukæmia, and remissions from three to twelve months have been obtained. T.E.M. has not proved of value in Hodgkin's disease, multiple myeloma, or in any form of carcinoma with the exception of some patients with bronchial carcinoma where favourable results have been reported. Myleran (Haddow) has given promising palliation in chronic myeloid leukæmia for periods up to two years and is so far the only substance which can be considered as a substitute for radiotherapy.

In acute leukæmias, folic acid antagonists (Aminopterin and related compounds) have given sporadically some temporary remissions in children. These substances, however, are of great toxicity and their use is not justified as the remissions are of very short duration. Similar short remissions can be obtained without toxic effects by using ACTH or cortisone.

Hormones

Cancer of the breast and prostate are to date the only neoplasms where control of the disease can be achieved by hormones. The effect of hormones is palliative and temporary. Nevertheless it remains the greatest advance, so far, in the treatment of disseminated cancer in these sites, previously quite untreatable.

The value of hormones is limited to a proportion of patients as some neoplasms are hormone resistant. Œstrogens are useful in cancer of the prostate and in cancer of the breast in women but not in men. The use of œstrogens is further restricted to the older age group, well past the menopause. In pre-menopausal women and at the menopause, œstrogens are not advisable and in some patients produce acceleration of growth. Androgens are of value in mammary cancer in women but not in men. Both androgens and œstrogens can produce regression of the primary growth, and of metastasis both visceral and skeletal. Hormone dependence is not a permanent character of breast and mammary cancer and, in many patients, the tumours at first dependent become hormone resistant. All these observations indicate that although temporary control of the tumours can be achieved, it is unlikely that hormonal treatment will result in complete and permanent eradication of the disease. Control has been achieved for periods varying from three months to two years in most cases and in a few up to five years. Increased doses of hormones do not often result in increased periods of control.

For the past three and a half years bilateral adrenalectomy has been made possible by the availability of cortisone. More recently hormonal control by hypophysectomy has been proved to be a practical procedure. Both these major surgical procedures are at present undertaken in patients who are no longer benefited by the simpler methods of hormonal treatment and in whom the disease is widely disseminated. The choice between administration of hormones and adrenalectomy or hypophysectomy depends at present chiefly on the extent of the disease and the fact that there is no clinical or laboratory method by which the hormone-dependent cancer can be differentiated from the hormone-resistant one. Further, it is as yet too early to say how long the palliative effects of adrenalectomy or hypophysectomy are likely to last. If prolongation of life is limited to two or three years, postponement of the major surgical procedure is indicated as long as other methods of treatment are effective.

The most remarkable feature is the alleviation of pain obtained by hormones, especially in skeletal metastasis. Relief from pain is achieved very rapidly, in a few days; the mechanism of this is not understood.

Pain-relieving Drugs

In the terminal stages of cancer the need for pain-relieving drugs is essential; of these morphia and its derivatives remain the most important. Their use, however, should be postponed as long as other remedies can offer alleviation. Skeletal pain can be relieved by palliative X-ray therapy. Uncontrollable pain from involvement of nerves can be achieved by injections of nerves, cordotomy or leucotomy. Morphia and its derivatives should remain the last resort and their function in the end is to help the patient to die and, in massive doses, morphia shortens life.

The management of advanced cases of cancer is nearly always the responsibility of the family doctor. Specialized forms of treatment are of importance and often of value but the risks, discomforts and disabilities not infrequently associated with such treatment need to be considered from the general background of the individual patient, his mental distress, his fear of treatment which often is greater than the fear of the disease, the desire to live, the severity of symptoms, the age and the likely expectation of life.

The Management of Advanced Cancer

By Richard Asher, M.D., F.R.C.P.

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I HAVE no experience of treating advanced cancer beyond that which falls to the lot of any general physician. In cases of advanced cancer surgeons and physicians can give each other much assistance.

The technical advances of surgery and anæsthesia allow much more massive surgical removals to be done and the discovery of new hormones allow more and more of the endocrine system to be taken away without killing the patient. I think it was Sir Henry Cohen who remarked here once "The feasibility of an operation is no indication for its performance", so, while admiring the skill of these surgical feats we must also pause to examine the fruits of victory and decide if they are worth the fight.

Firstly, radical surgery. In advanced cancer this is rarely possible. In deciding whether to attempt it, it is worth considering the mode of death without surgical treatment; death from carcinoma of the œsophagus for instance is so particularly unpleasant that there is much to favour attempting even a hazardous case. Another point concerns the common-ness of a disease. Carcinoma of the lung is so common that doubtfully operable cases should not be sent to the thoracic surgery units when chest clinics and mass X-ray units are already finding so many early cases. If a man is pretty certain to die soon, the fewer bronchoscopies, bronchographies, biopsies and chest operations he has in his last few months the better.

Secondly, palliative surgery—the severity of the symptoms which the operation is designed to palliate is the important factor. Jaundice, for instance, is sometimes a distressing death and cholecystogastrostomy well worth while. When I was a student Russell Howard taught us "It doesn't matter whether you die white or die yellow, but nobody likes to die scratching"; he thought the skin irritation the important thing but probably the other symptoms of jaundice including the depression are worth relieving in most cases. On the other hand a colostomy may sometimes produce as much distress as it relieves. Each case for palliative surgery is a separate problem and the doctor has to ask himself: How much distress is there? How much relief is the operation likely to give? How much distress is the operation likely to produce?

Radiotherapy

Though often responsible for many brilliant results radiotherapy has its disadvantages. First, some people guess they are suffering from cancer if they are treated with deep X-rays. Secondly, there are often severe general malaise and uncomfortable skin reactions. In my experience people with carcinoma of the lung often react badly to radiotherapy and the little span of life allotted to them is made less tolerable without being lengthened. The exception is where there is superior mediastinal obstruction. The relief of this by radiotherapy can be dramatically rewarding.

If one includes chronic leukæmias among the cancers I would observe here that radio-therapy should not be used too early, unless a patient's splenomegaly or adenopathy are mechanically a nuisance to him and unless he is anæmic. There is little point in producing dramatic changes in the size of his spleen or the number of his white cells, impressive though these are on paper. "Don't treat blood counts treat patients" is the motto. Many leukæmic people, particularly the chronic lymphatics, can attend for six-monthly observation without any treatment for several years, free of symptoms and in ignorance of the diagnosis.

The Hormone-dependent Cancers

It is now recognized that cancers of the breast and prostate in some way depend for their existence upon sex hormones manufactured in the suprarenal glands and the gonads. Bilateral suprarenalectomy with or without gonadectomy has, in certain cases, given remarkable results. What little I know about it is from Sir Stanford Cade's Hunterian lecture. In favour of this latest advance in endocrine surgery is that it is only used in cases of otherwise hopeless prognosis and that about 1 in 5 (9 out of 46 cases of disseminated breast cancer) of those operated on make a really dramatic (though not permanent) recovery. Furthermore the knowledge of the endocrine physiology of certain cancers which is being gained all the time is a very valuable asset to everyone fighting against cancer.

Yet there are also certain points against the operations: (1) Patients have to submit to fairly extensive and risky operations whose result is so uncertain that it is just as likely not to benefit as to benefit them. (2) The operation leaves them dependent on an expensive and scarce drug, cortisone. (3) It may improve the patient only for a brief while and so give him the sorrows of downward progress on two occasions instead of one.

In summary, it certainly represents an advance in knowledge: the operation seems ethically justifiable, but it cannot yet justify the term "satisfactory treatment".

Lastly there is the purely medical approach which consists in managing the patient's journey to the grave in the way which gives him the greatest physical and mental comfort. Until active treatment is more uniformly successful most cases of advanced cancer will have to be treated in that way, so it is worth saying a little about it. First should the patient be told he has cancer and is dying? It is my experience that people as a whole are far happier if they do not know. Some of them I feel sure know in their heart of hearts, but prefer to play a game of make-believe with the doctor: others remain in complete ignorance and modest contentment to the end. To assist in this beneficial deception it is important to avoid *sotto voce* murmurings at the foot of the bed or the use of words like tumour or carcinoma. Relatives, too, can play their part by a cheerful demeanour at the bedside; in fact there is something to be said for keeping relatives as well as patients in ignorance of the downhill progress until it becomes obvious.

A most important thing in managing these people is to treat their minor complaints if anything more assiduously than the one they are dying of. A patient with extensive carcinoma may worry about some wax in his ears or a fungus infection of his feet and by treating these we can sometimes both make him more comfortable and distract his attention from the major complaint.

Also if a hospital patient has only about a week to live it is unkind to transfer him from the acute medical ward, which he already knows, to a chronic ward where the nurses and patients are strangers to him.

For the relief of pain there is still probably little to touch the well-tried morphia or pethidine but they need not be given purely because a patient is going downhill from cancer, for sometimes it is a surprisingly painless progress; nor need the dose be increased automatically for some people seem to lose their pain towards the end and do not need to be kept continuously drugged. It is often wise to give the substances by mouth so that the patient is less aware of being drugged than if injections are given.

To sum up: The endocrine surgery of extensive cancer is a great advance, but at present more of an advance in knowledge than an advance in treatment.

If it is highly probable that a patient is going to die in a few months, the less operations and investigations he has to submit to in that time, the better.

Prolongation of life is not the only aim of treatment; it should be a tolerable life. It is better to be wholly alive for one month than half alive for two.

It is not always worth the discomforts of major surgery to get minor recovery.

It is better to go steadily downhill towards death than to pursue an undulating course to the grave buoyed up by temporary recoveries.

The Use and Limitations of Skin Tests in Asthma

By R. S. BRUCE PEARSON, D.M., F.R.C.P.

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SKIN tests offer no short cut to the diagnosis or treatment of asthma. Their use is limited and the technique of testing though simple must be precisely carried out, to achieve reasonable results. The following remarks apply mainly to tests carried out with inhalant allergens: food tests, which present special difficulties of their own, are not considered here.

Table I shows a comparison between the results of skin testing in asthmatic patients and a carefully selected control group (Pearson, 1937). The figures indicate the percentage of reactions obtained when these two groups were tested with two common inhalant allergens

TABLE I.—COMPARISON BETWEEN SKIN REACTIONS IN ASTHMATIC AND CONTROL SUBJECTS

	No.	Horse dander	Chicken feather	Horse serum
Asthmatics	148	60%	51%	8%
Controls	190	12%	15%	2%

(horse dander and chicken feathers), and with horse serum albumin, a pure protein with which the majority of people are unlikely to have come in contact. The extracts were standardized by their nitrogen content (2 mg. %) and were in a suitable strength for testing purposes. The tests were carried out intradermally and a positive reaction was considered to be shown by an increase in the size of the wheal and a reflex flare: doubtful or small reactions indicated by a flare only are excluded. Positive skin tests were obtained in a number of persons who were not themselves suffering from allergic (atopic) disease but many more reactions were obtained in the asthmatic group. It was also shown that a greater number of large reactions were given by asthmatics. The control group was carefully selected to exclude all those who had in the past suffered from asthma, rhinorrhœa or any other recognized allergic (atopic) disorder, and those with a family history of these conditions. If such individuals are also included the proportion giving positive reactions is increased for the three test substances to 19%, 19%, 3% respectively.

These findings indicate that there is no fundamental difference between those suffering from asthma and those who have never manifested any form of allergic disorder. The difference between the two groups at least as far as skin testing is concerned is quantitative only, and if we are fortunate enough not to have suffered so far from allergic (atopic) disorders we may still be examples of latent or potential allergy, which may one day become manifest with production of symptoms. This point of view is confirmed by a number of observations. Salen and Juhlin-Dannfelt (1935) have shown that men whose work brings them into contact with horses will tend to give positive reactions to horse dander, whereas millers will more often become skin sensitive to flour, although these skin-positive individuals do not necessarily develop symptoms. We all pass through a phase of sensitization to the bites of insects, though there will be individual differences in the degree of sensitivity achieved.

We may also draw a parallel with the tuberculin test. A positive Mantoux does not mean that the reactor is suffering from active tuberculosis but only that he has at some time been infected by the tubercle bacillus, often without other evidence of infection at any time.

TABLE II.—CORRELATION BETWEEN CLINICAL HISTORY AND SKIN TESTS

	Cases tested	History+ve Skin test+ve	History—ve Skin test—ve	History+ve Skin test—ve	History—ve Skin test+ve
Grass pollen	200	27%	57·5%	3%	12·5%
Cat hair	200	7%	74·5%	2·5%	16%
House dust	200	29·5%	33%	4·5%	33%

Table II refers to the correlation between the clinical history and the skin tests in asthma. The tests were carried out at two hospitals with two different proprietary brands of extract. Tests to pollen were carried out by the prick method in nearly every instance and those to cat hair and house-dust extract by the intradermal technique. 200 cases were included in each group. They were unselected except that a few patients with a definite confirmed pollen allergy were not invariably tested with other materials, and elderly patients with a long-standing history of bronchitis preceding their asthma were not always subjected to skin tests.

The test substances (pollen, cat hair and house dust) were for the following reasons:

(1) Grass pollen. Sensitization to this material can, as a rule, be readily detected from the history owing to its seasonal appearance. The doctor may suspect it even when the patient has not appreciated its significance. It is reasonable to expect a high correlation between skin tests and history.

(2) Cat hair is included because cats are common pets and sensitivity to their hair and dander is likely to be recognized. One is here dependent on the patient's observations alone and would not therefore expect so high a correlation between the history and the presence of positive reactions.

(3) House dust is everywhere; it appears to be highly antigenic and therefore likely to play an important part in producing asthmatic symptoms. Its universal distribution is a reason for expecting that it will often escape recognition by the patient as a causative agent. For the purpose of these observations it does not matter whether dust extracts are considered to be a mixture of allergens or to contain a single antigenic substance.

Table II shows that these expectations are well borne out. 27% of patients gave a history suggestive of grass pollen sensitivity and also gave positive skin reactions. 3% only were thought to be pollen sensitive and found to have negative skin tests. On the other hand 70% gave no history of sensitization, and 17·9% of these (12·5% of the total) gave positive

reactions. The first two columns in Table II, in which history and skin tests agree, together amount to 84·5% of the total.

With cat hair the findings are very similar. A smaller number of patients gave a positive history of sensitization (7%) and a relatively greater proportion (16%) gave positive skin tests without a confirmatory history, but there was agreement between the history and the result of the tests in 81·5%.

House dust gave the highest number of positive tests (62·5%) but clinical confirmation at the time of testing was only obtained in approximately half and, as one would expect, women recognized the association between dust and asthmatic symptoms more commonly than men, though both were approximately equally affected.

These figures suggest that though not all positive reactions indicate a clinical sensitivity, skin tests may be useful in the following ways: They may (1) Confirm a suggestive history. (2) Demonstrate by failure to cause a reaction that the patient is not sensitive to a particular substance. (3) Suggest that a material previously unsuspected by the patient may be a cause of symptoms. It is in this third group that the tests may prove most helpful since they may give a lead which the history has not suggested and which subsequent observation may prove to be correct.

Many factors environmental, constitutional and technical may influence the results of skin tests:

(1) *Environmental factors.*—(a) The temperature of the outside air. Tests will develop and pass off more rapidly on a hot day. If the patient is cold he may fail to react. (b) The previous administration of adrenaline-like or antihistamine substances will abolish or reduce positive reactions.

(2) *Constitutional factors.*—(a) Some patients will react to any form of trauma possibly as the result of liberation of histamine. They will produce a response to control saline injections, and this fact must obviously be taken into consideration in interpreting the results. (b) Patients may feel faint during testing and this, probably due to a fall in blood pressure, will diminish the size of positive reactions or abolish them altogether.

(3) *Technical factors.*—(a) The volume of testing fluid injected is of great importance. It is generally recognized that 0·02 ml. is the maximum volume to be injected intradermally. Injections of larger volumes than this will give rise to false positive reactions because of traumatic effects leading to the non-specific liberation of histamine. (b) The nature of the test material is of great importance. Unfortunately only very few firms make more than a very superficial attempt to standardize their extracts. These may and sometimes do contain histamine or other non-specific irritant substances. Other materials may be inert. Only familiarity with the products of various firms and frequent counterchecking can overcome this difficulty. Improved standardization will make for more reliable results. (c) The test site should be inspected repeatedly in the half-hour after the test has been carried out. (d) Due allowance must be made for the method of testing used; the intradermal method is more sensitive and will produce more positive reactions than the prick or scratch.

Clearly familiarity with the technique of testing is necessary to obtain reliable results, and the more standardized the conditions under which the tests are carried out the more consistent will the results be.

In conclusion skin tests with inhalant allergens in asthmatic subjects have proved a helpful means of investigating the underlying cause. As with all other laboratory tests they have their limitations, they require a standardized technique, and they must be considered in conjunction with the history of the patient and the subsequent course of the disease.

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The Uses and Limitations of Skin Tests in Asthma

By A. G. OGILVIE, M.D., F.R.C.P.

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As a general physician, who has to deal with asthmatic patients, I have used these skin tests for a number of years. I am, however, not an allergist. In fact, it is with some difficulty that I pronounce the names "Prausnitz-Küstner".

These tests are merely aids to diagnosis. We must not expect too much from any diagnostic procedure. We should, however, expect to get some useful information, however limited, and which will be reliable in most of the cases.

In judging the value and accuracy of any such "method of precision", adequate criteria are essential. Materials, methods and recording require to be standardized (often after much

trial and error). We are then able to assess the worth of a particular reaction for our purpose, as, for example, the tuberculin-testing procedure. The solutions and the technique are standard, and the results are recorded according to widely agreed criteria. This value is consequently accepted, so that the treatment of any patient as tuberculous without a positive skin test can rarely be justified, unless the bacillus has been isolated.

In my view, skin tests in asthma are not in this category. The position is too fluid.

Four methods of application are variably employed, extracts standardized according to no widely accepted or truly reliable techniques, varying considerably in potency, are used, and the results are recorded according to no standard criteria.

Under these circumstances, the recording of results must often be a mere matter of nomenclature. No analytical estimate of their value is possible.

Cooke (1947) states: "Reactions are graded according to arbitrary standards which each worker adopts for his own purposes."

Vaughan and Black (1934, p. 182): "Certain portions of skin appear to be more reactive at a given time than others. This being true, one must admit that in the presence of frank allergy to a given substance the reaction may vary at a given time, anywhere from negative to sharply positive."

Rackemann (1951) states: "When the history and the skin tests do not agree, the history should be the guide." We may now consider the standardization of extracts. Vaughan and Black (1934, p. 269): "There is still no unanimity of opinion with regard to the merits of the total nitrogen standard, and the protein nitrogen standard. Bowman has presented evidence that the latter is not as reliable as claimed ... an extract which contained 65% as much protein nitrogen as another standard extract only showed 10% as much activity by skin test."

Standardization by clinical testing, as carried out in this country, is probably much better than this on the whole, but from what has been quoted on the variability of the skin reactions, it would appear to have its drawbacks. One firm in this country, manufacturing extracts for skin testing, is, in fact, working on a new standard of potency based on a principle entirely different from any at present in use. If successful, this may well alter the position by giving us a basis on which to standardize technique and recording.

With variable technique, unreliable extracts, and no widely recognized criteria for recording results, interpretation is difficult. Here are a few implications which we should consider when deciding on the result of skin tests: (1) When it is a question of depriving a child of a well-loved animal.

(2) When it is a question of altering the diet, and particularly the diet of a growing child. I well recall seeing a boy of 12 in a condition of emaciation after several months on a diet based on such evidence. The details of the diet are not now so clear in my mind as they were, but the most emphasized constituents were water biscuits and water. (The asthma was very severe when I saw him.)

(3) When it is a question of advising a young man as to a career, or the parents of a child on the choice of a school, are our answers to be based on skin testing?

Indiscriminate and routine skin testing is unhelpful in the diagnosis of asthma, and may well be misleading; but this is not to condemn the method out of hand.

If a sheep-farmer develops severe asthma on contact with sheep or horses, is he to be advised to sell out and take to insurance work when other methods fail to relieve him? And is a man whose every summer is made a purgatory due to pollen sensitivity, and who responds no longer to antihistamine treatment, to be advised to live at the top of Mont Blanc?

Though skin-testing may mislead, and so-called "desensitization" may fail, the attempt should certainly be made. Experience shows that success with such clear-cut indications is not at all infrequent.

To sum up, used with discrimination in selected cases, and with recognition of its admittedly serious limitations, skin-testing can be useful in the diagnosis of the asthmatic. Used in a routine fashion without selection, it is quite likely to mislead, and most unlikely to be helpful, however much it may impress the patient or the parent.

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JOINT MEETING No. 2

Section of Ophthalmology with Section of the History of Medicine

Chairman—HUMPHREY NEAME, F.R.C.S.

(President of the Section of Ophthalmology)

[*December 9, 1954*]

An Ophthalmic Case-book of Eighty Years Ago

By THE HON. G. J. O. BRIDGEMAN, F.R.C.S.

ABOUT a year before the outbreak of the last war the Secretary of St. George's Hospital told me that it had been decided, owing to shortage of space, to destroy all in-patient records dating back more than thirty years. I went with him to the store-room and obtained possession of the oldest volume of ophthalmic case-notes which I could find. It contains the records of the female eye ward from October 30, 1867, to March 15, 1871. During this period the ophthalmic work was undertaken first by Mr. Henry Power and later by Mr. Robert Brudenell Carter, and for the following biographical notes I am indebted mainly to Plarr's Lives of the Fellows of the Royal College of Surgeons of England, Power's autobiography, and a paper on Brudenell Carter by Mr. R. R. James which appeared in the *British Journal of Ophthalmology* of June 1941 (**25**, 330).

Henry Power was born in 1829, the son of an officer in the 35th Foot which regiment was then under orders for Barbados. In the great West Indian hurricane of 1831, which killed the sergeant-major, a sergeant and five privates of the regiment, Power was buried in his pram but was rescued unhurt. (The same hurricane, curiously enough, very nearly killed Haynes Walton who afterwards became Ophthalmic Surgeon to St. Mary's Hospital.) Power qualified from St. Bartholomew's in 1851 and was on the active staff of the Royal Westminster Ophthalmic Hospital from 1855 to 1889. He was also assistant surgeon to

FIG. 1.—Henry Power. (Reproduced by kind permission of Air Vice-Marshal D'Arcy Power.)

the Westminster Hospital from 1857 to 1867 when he decided to confine himself to ophthalmic surgery and was appointed to the newly-created post of ophthalmic surgeon to St. George's Hospital in the latter year, and this case-book dates from then. He was also for twelve years eye surgeon to St. Bartholomew's Hospital, Rochester, going down there every Wednesday by the 2.0 o'clock train and returning by the 6.30 boat train in the evening. St. Bartholomew's Hospital followed the example of St. George's in July 1870 and Power

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resigned from the latter on appointment to his old hospital which he served for twenty-six years. He was closely connected with the Royal College of Surgeons, acting for many years as an examiner, and held most of the lectureships at one time or another: he was a member of the Council of the College, and Vice-president in 1885. He was President of the Ophthalmological Society of the United Kingdom 1890–93. He was also for twenty-three years lecturer in physiology at the Royal Veterinary College. Henry Power was a fine ophthalmologist and a good teacher, and was highly respected by those with whom he came in contact, both professionally and otherwise, for it is on record that when he died in 1911 at Whitby (where he had gone to live on his retirement) nearly all the tradesmen along the route closed their shops on the day of his funeral, although it was market day.

FIG. 2.—Brudenell Carter. (Reproduced from Burton Chance, 1935, *Arch. Ophthal.*, *Chicago*, **13**, 348, by kind permission.)

His successor, Robert Brudenell Carter (1828–1918), was a personality of somewhat different type—rather like Power, his energies were by no means exclusively devoted to ophthalmology. He was named Robert Brudenell after his father's friend and neighbour the 6th Lord Cardigan, father of Cardigan of the Light Brigade. After qualifying from the London Hospital in 1851 he volunteered as a surgeon in the Crimean War and served with the Turkish Army. W. H. Russell, *The Times* War Correspondent, was a friend of his, and Carter wrote a number of letters from the front which were published in that newspaper. He received both the British and Turkish medals for the campaign. On return he took part in establishing the Nottingham Eye Infirmary and later the Gloucestershire Eye Hospital. At the age of 40 he applied for employment with *The Times*, describing himself as "a conspicuously unsuccessful general practitioner in the country", and was put on the staff. He contributed articles to *The Times*, as also to the *Lancet*, over a long period in a clear if somewhat forceful style. He was elected a member of the first L.C.C. but failed to secure re-election. There are a number of anecdotes about him. He is supposed to have said "all ophthalmic surgeons should be ambidextrous; it is surprising how many are ambisinistrous". On one occasion he was deputed by the Council of the Royal College of Surgeons to attend the annual meeting of the Members of the College. When his turn came to speak the audience listened in silence until he made a remark which set the whole meeting in an uproar. Carter remained standing on the platform in an attitude as though watching a cageful of agitated monkeys, and when the disturbance died down he quietly and deliberately made exactly the same remark again. During his membership of the General Medical Council he was responsible for the suggestion that sentence on those found guilty of less serious offences should be postponed till the following session, and it is to Brudenell Carter that many a medical man owes his escape from the penalty of removal from the Register. The post of Ophthalmic Surgeon at St. George's was held by him from 1870 till his retirement in 1892, and he was in charge of about the last forty-odd cases in this book.

During the whole of this period 225 patients were admitted and 16 readmitted to the female eye ward, of whom 15 were small boys. The oldest patient was 83 and the youngest 3 months. 8 cases were discharged at their own or their parents' request. There is considerable variation in the amount of detail and completeness of the individual records, but some sort of diagnosis is given or can be inferred in nearly every instance. There are about five or six different handwritings in this book; Air Vice-Marshal D'Arcy Power identified that of his grandfather in some of the more accurately recorded cases, including one with a rather neat little coloured drawing. References to the visual acuity are scanty and rather indefinite. "Strumous" and "rheumatic" ophthalmia and "scrofulous" keratitis are among the terms used. A summary is shown in Table I. The number of cases of superficial inflammation of the conjunctiva and cornea is of some significance. The age is stated in 96 of the 102, and 80 of these were under 21. 11 patients are recorded as having "granular lids", and almost certainly at least some of them must have been trachomatous. The lowered ratio of cases of superficial inflammatory conditions requiring admission to a

TABLE I

Injuries				14	Glaucoma				9
Lacrimal conditions				8	Squint				16
Lid conditions				18	Miscellaneous				16
Conjunctivitis and keratitis			102					—
Uveitis				19					225
Cataract				23					

London hospital nowadays evidently reflects the improvement in social conditions and ocular hygiene in this country during the past eighty or ninety years.

On one occasion the writer lapses from the purely objective style—Case 191. Bilateral corneal leucoma. "This patient is afflicted with deafness and dullness of vision which is only equalled by that of her intellect."

There is a detailed account of a boy aged 4, admitted three months after an enucleation (performed elsewhere) with an extensive neoplastic mass in the orbit, which fungated. The measures adopted to deal with this were not a little heroic; acetic acid was injected four times, Condy's fluid and ferric chloride applied to the surface, and the mass was ligatured on several occasions. The child died after 116 days; post-mortem revealed direct extension into the brain and metastases in liver and one lung. The microscopic report was indefinite. There was one other death in the series, a young woman of 25 who was under observation for papillœdema and who died rather suddenly. The diagnosis was doubtful, and the post-mortem was not contributory. There was probably one other case of neoplasm, in a child aged 10 months with a bilateral dun-coloured mass protruding from each fundus. Enucleation was refused by the mother and there is no further record of the case. One young woman while awaiting iridectomy developed scarlet fever and subsequently smallpox. On readmission to the eye ward the notes state that she "does not seem much the worse".

In the therapeutics of that period, quinine figures prominently. Prescriptions for quinine in one form or another appear 106 times in the book. There was a good deal of purging, frequently by pulv. jalapæ co. or by calomel. There are twelve different prescriptions containing mercury in one form or another, and this drug was prescribed 107 times in this series of cases. Calomel was applied locally in 12 cases, nearly all of which were keratitis in some form. Aconite-and-colchicum seems to have been thought a useful combination by Mr. Power and this was given in a number of conditions, especially "rheumatic" iritis. Leeches, as many as six in one instance, were ordered for 27 patients, mainly those with inflammations of cornea and iris.

Much less use seems to have been made of atropine compared with modern practice; it was ordered for 37 patients only, although there were over 40 cases of keratitis, and 19 of uveitis, not to mention post-operative conditions.

Calabar bean was exhibited in 4 cases but none of them had glaucoma. Vinum opii was ordered to be dropped in the eye in 8 instances—1 acute conjunctivitis, 3 corneal ulcers, 1 keratitis, 1 endophthalmitis and 2 abscesses of the lacrimal sac—all active inflammatory conditions. Relief is noted in every case.

With regard to surgery, 78 operations are recorded. 13 cataracts were apparently removed by extracapsular and 1 by intracapsular technique, 2 were couched, there was 1 curette evacuation, and 6 discissions. The scoop was used once. The change-over from making the corneal section with a Beer's knife, according to the purpose for which that instrument was designed, to a Graefe knife took place in this series about the end of 1869.

Of the iridectomies 4 were performed for glaucoma, and in the remaining 17 instances a bilateral operation, usually for optical purposes, was carried out *on the same occasion* in no less than 8 cases, 1 of whom was the youngest in the series, aged 3 months. Bilateral subconjunctival tenotomies were also performed at the same sitting on 2 of the 10 squints which had surgery. In 1 of the latter an over-corrected convergent squint underwent a second operation. A seton was used in 8 cases. Abscission of the globe was done on 2 occasions. (This operation, which consisted in amputating the anterior segment of the eye and closing the remainder with sutures, went out of favour about this time or slightly later because of the danger of sympathetic ophthalmia. There is no definite diagnosis of this latter disease in the series, although anyone reading the notes of certain cases of injury in children might perhaps wonder whether something of the sort was not in fact occurring.)

There were 4 cases of post-operative erysipelas and, considering the extent of the ignorance at that time regarding control of wound infection, the absence of reluctance to operate on both eyes at one sitting is rather remarkable. A possible explanation may have been the difficulty in persuading patients to submit to surgery a second time, which in turn may be attributable to the limitations of anæsthetics at that period. Cocaine did not come into use as a local anæsthetic before 1884. The only substance actually employed for the purpose of anæsthesia in this series was chloroform, which is noted as having been administered in 9 cases, but this was probably done as a routine because in 2 instances—a woman of 22 who

had a congenital cataract couched and 1 of 57 who had lens extraction with iridectomy—it is specifically stated that chloroform was *not* used.   One cataract patient had a weak heart, and it was thought unsafe to push the anæsthetic to the point where the orbicularis muscle relaxed; Mr. Power consequently made his incision downwards. "The entire operation was satisfactorily performed."

However much has changed in the practice of ophthalmology during the past eighty years there are some things which are and always will be the same.   The last clinical note in this book reads as follows:

"21st March 1871.   The yellow ointment produced great pain and irritation.   To be left off."

I would like to acknowledge the assistance received in preparing this paper from Mr. Sheridan Lefanu, Librarian of the Royal College of Surgeons, from Air Vice-Marshal D'Arcy Power, and from my old teacher, predecessor and friend, Mr. R. R. James.

Leonardo da Vinci on Vision
By K. D. KEELE, M.D., F.R.C.P.

LEONARDO's interest in light and vision was primarily that of an artist for whom accurate observation was a passion.   And in this connexion it may be recalled that it was the artists, not the philosophers of the Renaissance who introduced the accurate observation necessary for the foundation of such sciences as anatomy.

The eye had been frequently studied before him.   Alcmaeon, Democritus, Plato and Aristotle had all advanced theories of vision.   Of these Plato's remained the most popular in that it combined the two main antagonistic theories, one that vision resulted from images entering the eye; the other that a stream flowed from the eye to the object like a lantern beam.   Herophilus of Alexandria, about 300 B.C., had described the anatomy of the eyeball, optic nerve and retina; Galen had accepted most of this anatomy and located the visual faculty in the lens in the centre of the eye.

Aristotle's theory of vision points out the importance of the medium connecting the eye and object, emphasizing that since this might consist of air, water or other substances like glass, &c., all these must have the property of translucency, possessed by a substance itself permeating all such media; this he called the diaphanous—a precursor of Newton's ether. Upon this diaphanous were impressed those images which, entering the eye, produced vision.   There was no necessity therefore for visual emanations.   Until Leonardo's time all had agreed that light or the power of vision flowed in corpuscular streams.   With Leonardo a wave conception of light was launched in the following words: "Just as the stone thrown into water becomes the centre and cause of various circles, and sound made in the air spreads out in circles, so every body placed within the luminous air spreads itself out in circles and fills the surrounding parts with an infinite number of images of itself, and appears all in all and all in each part." (A.10r.)

Leonardo uses the Aristotelian term "species" and the Aristotelian concepts of light, allowing the emanation theory only for the "beguiling power of a maiden's eyes".   "The senses when they received the species of things do not send forth from themselves any power, but the air between the object and the sense incorporates in itself the species of things and by contact with the sense presents them to it."   (C.A.90.)

By this theory the air in daylight is filled with the images of things radiating and intersecting in straight lines, along which the species or images enter the eye; taking the shortest course in accordance with Aristotle's law that every natural action is performed in the shortest way.

Both the laws of reflection of light, and the existence, though not the laws of, refraction were known to Leonardo from the writings of the Arab physicist Alhazen of the eleventh century.

Thus when he comes to make a schematic drawing of the eye the rays are shown refracted according to the rule "the rays of the images approach the perpendicular when they pass from the thin to the dense".   That Leonardo did not fathom the underlying laws of refraction in different media is not surprising when it is realized that though so firmly believing "in the certainty of mathematics" he himself was acquainted with little arithmetic, and knew no algebra, or trigonometry.

Leonardo's approach to the study of the anatomy of the eyeball was typically ingenious — "in the anatomy of the eye, in order to be able to see the inside well without spilling its humour, you should place the complete eye in white of egg and boil it until it becomes solid, cutting the egg and the eye transversely so that no part of the middle portion is poured out".   (K.119.)

This is one of the earliest examples of the technique of imbedding tissue for section-cutting. But unfortunately it does not seem to have been a great success, for Leonardo, like those before him, still found the lens to be a round object in the centre of the eye. Indeed this may have resulted from the very ingenuity of the method, for according to Argentieri if the lens is boiled it will always appear round, and in the dead eye it always drops away from the iris.

In the descriptions of the eyeball by Galen and Avicenna, the membranes of the brain surrounding the optic nerve expand to enclose the humours and contents of the eye, and so form the coats of the eyeball.

Leonardo preserves this general plan but shows little interest in the various coats; most of his diagrams focus on the cornea, pupil, lens and optic nerve. In all his figures the paths of light rays are shown crossing once behind the pupil whence they pass into the lens; there they cross once more, to impinge on the optic nerve (Fig. 1).
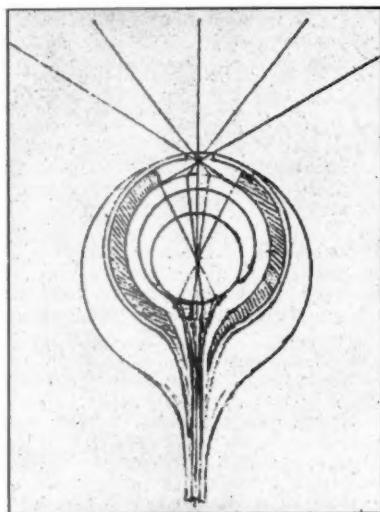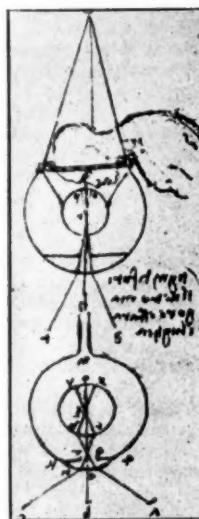

FIG. 1. FIG. 2.

FIG. 1.—Schematic figure, drawn by Leonardo to show the path followed by light rays within the eye. These are shown to cross twice; once as they enter through the pupil, and again on their path through the central, round lens. Finally they impinge on the expanded end of the optic nerve where Leonardo located the power of vision. (C.A.337.)

FIG. 2.—Leonardo's experiment in which the human eye takes the place of the optic nerve in a glass model of the eyeball with its lens, the whole apparatus being made to fit on to the head of the observer. A diagram of the paths of light through the eye is drawn below, the corresponding paths of light in the model above. (D.3.)

(Leonardo wrote left handed and mirrorwise, that is, right to left, this explains the unusual lettering of some of the illustrations.)

Thus, according to Leonardo, there is an inversion of the image in front of the lens, and a second inversion within the lens, so that the final upright image is presented to the end of the optic nerve, where he considered lay the faculty of vision.

Erroneous as this thesis is he founds it on a number of observations and experiments, all of which are governed by the necessity, as he calls it, for two intersections in order that the final image shall be upright. It was inconceivable to Leonardo that the image carried by the optic nerve should be inverted.

His most ambitious experiment consists of constructing an artificial eye—out of a glass globe filled with water, within which is a smaller glass lens, attached to a kind of box (Fig. 2). The whole is fitted over the observer's head "as far as the eyes". The observer's eye is then made to take the place of the optic nerve or "power of vision". "Such an instrument", he says, "will bring the species to the eye, just as the eye brings them to the visual power". (D iv.)

On the upper part of the page Leonardo draws the model, beneath which he draws the

passage of the main light rays, noting that the power of vision lies in the optic nerve behind, and pointing out the necessity for two intersections of the rays.

A second modification of this method of studying the path of the light rays involves placing the eye in a square box with an aperture representing the pupil, behind which is a glass ball representing the lens. Again, the position of the optic nerve is occupied by a human eye. Here we begin to see how closely Leonardo's study of the eye was linked to his discovery of the camera obscura.

This is most clearly illustrated in a page of manuscript (D.8r) where the passage of light rays through the cornea, pupil and lens is represented at the top whilst below is the comparable scheme in a camera obscura with a sheet of paper inserted like a film to pick up the reversed image from without.

The first clear description of the camera obscura is written on this page in the following words: "Experience which shows that objects transmit their images or likeness intersected within the eye in the albugineous humour, shows what happens when the images of the illuminated objects penetrate through some small round hole into a dark habitation. You will then receive these images on a sheet of white paper inside this habitation somewhat near to this small hole, and you will see all the aforesaid objects on this paper with their true shapes and colours, but they will be less, and they will be upside down because of the said intersection.

"The images if they proceed from a place that is lit by the sun will actually seem painted on this paper, which should be very thin and seen in reverse, and the said hole should be made in a very thin sheet of iron. Let a, b, c, d, e, be the said objects lit by the sun (Fig. 3), o, x, be the front of the dark habitation in which is the said hole at n, m; s, t, the said paper where the rays of the images of these objects inverted are cut, for as their rays are straight, a, which is right becomes left at k, and e, which is left becomes right at f, and so it is within the pupil." (D.8r.)

Leonardo uses the word "luce" at times to describe the aperture in the iris; at other times the word includes the whole system of cornea and iris, with its aperture the pupil. "Nature has made the surface of the pupil situated in the eye convex in form so that surrounding objects may imprint their images at greater angles than could happen if the eye were flat." (D.1r.)

This he verified by another experiment:

"In order to see what function the cornea has to the pupil, have a thing resembling this cornea made out of glass."

Several such models are drawn, the most interesting of which also illustrates Leonardo's favourite procedure of looking at objects through a pinhole in a piece of paper, in order to isolate narrow beams of light. One of these is shown passing through the cornea and the pupil (Fig. 4).

Not content with this, he makes another model, large enough to look through—"if you take a half a ball of glass, fill it with water, and put it close to your face, you will see all the things that can be seen from the surface of the ball; in such a way you will be able to look straight at your own shoulders". (C.A.222r.)

Thus he found that the visual field was greater than 180 degrees—an observation which he illustrated by several drawings.

He then points out that all images throughout this wide field of vision are not seen with equal clarity. Maximal precision he holds occurs with the beam that travels along the optical axis or "central line". The more a beam of light diverges from this the less clear the image. "The eye", he writes, "has only one central line, and all the things that come to the eye along this line are well seen. Around this line are infinite other lines which are so much less efficient as they are a greater distance from the central line." (Q.V.12v.)

In these words he accounts for the differences between central and peripheral vision.

The pupil itself received a great deal of attention from Leonardo. He was fascinated by its changes in size with light and darkness.

In the Forster Codex (158v) he describes how he noticed the pupil growing and shrinking "according to the brightness of its object" as a person emerged from darkness into light and vice versa. "This occurrence", he adds, "once deceived me in painting an eye; and that was how I learnt it."

Leonardo described both photophobia and the reaction of the pupil to light in these words, "The eye which is used to darkness is hurt on suddenly beholding the light and therefore closes quickly being unable to endure the light. This is due to the fact that the pupil in order to recognize any object in the darkness to which it has grown accustomed increases in size employing all its force to transmit to the receptive part the image of things in shadow. And the light, suddenly penetrating, causes the large part of the pupil which was in darkness to be hurt by the radiance which bursts upon it . . . and which seeks to maintain itself there, and will not quit its hold without inflicting injury to the eye.

"The pain caused to the eye in shadow by the sudden light arises from sudden contraction of the pupil, which does not occur except as the result of the sudden contact and friction of the sensitive parts of the eye." (C.16r.)
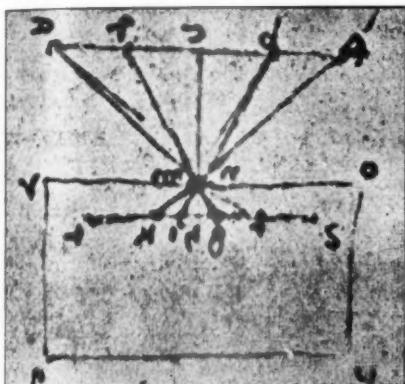

FIG. 3.

FIG. 4.

FIG. 3.—Diagram of the camera obscura and its aperture, to be compared with the eyeball and its pupil. Light rays are shown converging on the aperture m, n, and producing a reversed image on the sheet of paper s, t. (D.8r.)
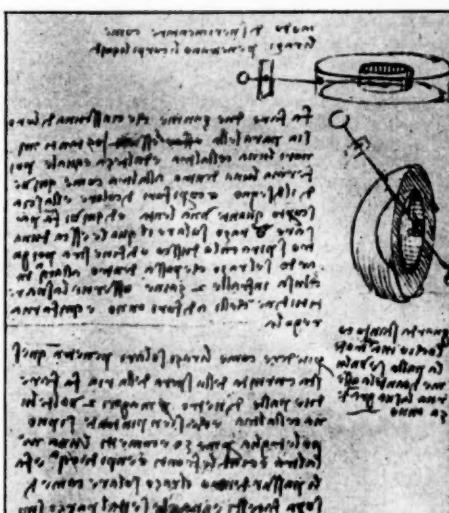
FIG. 4.—Glass models of the cornea through which isolated rays of light pass. Leonardo's method of isolating beams of light was by looking at a luminous object, such as a star, through a pinhole in a piece of paper, as here illustrated. (F.33v.)

The fine adjustments of the pupil in both man and animals were studied, and a hypothesis of night vision devised. "The pupil of the eye changes to as many different sizes as there are differences in the degrees of brightness. . . . Nature is here establishing a continual equilibrium perpetually adjusting and equalizing by making the pupil dilate or contract in proportion to the aforesaid brightness or obscurity which continually is presented to us. You will see the process in the case of nocturnal animals, like cats and owls, &c., which have a small pupil at midday and very large at night . . . and if you wish to make the experiment with men, look intently at the pupil of the eye while you hold a lighted candle at a little distance —— and you will see that the nearer the light approaches to it the more the pupil will contract." (D.5v.)

He accounts for the night vision of owls on the basis of the size of their pupils—"Such a pupil (the owl's) increasing in the night-time a hundred times more than that of man, sees a hundred times more light than man, so that the power of vision is not overcome by the darkness of night. And the pupil of man which only doubles its size, sees little light, and it is almost like that of a bat which does not fly in times of too much darkness". (An.B.13v.)

There can be no doubt that Leonardo appreciated the relation between light and the size of the pupil—a discovery which is attributed to Della Porta. But his own keen vision failed to detect the changes of the pupil with accommodation. These were not to be described until the experiments of Scheiner in 1631.

Leonardo had to wear glasses in his later years, and this may account for the fact that with regard to errors of refraction he makes no mention of myopia but describes his own presbyopia at some length.

Alongside a diagram in C.A.244 r.a. he writes on "A proof of the manner in which glasses aid sight" (Fig. 5).

"Let a, b, be the glasses and c, d, the eyes, and suppose these to have grown old. Whereas they used to see an object at e with great ease by turning their axes very considerably from the line of the optic nerves, now by reason of age the power of bending has become weakened

and consequently it cannot be twisted without causing great pain to the eyes, so that one is constrained of necessity to place the object further away, that is from e to f, so to see it better, but not in detail. But through the interposition of the spectacles the object is clearly discerned at the distance it was when the eyes were young, that is at e, and this comes about because the object e passes to the eye through various media namely rare and dense, the rare being the air that is between the spectacles and the object, and the dense being the thickness of the glass of the spectacles. Consequently the direction of the line of the rays bends in the thickness of the glass, and is twisted so that it sees the object at e, as though it were at f, with the advantage that the position of the eye with regard to its optic nerves is not strained, and by seeing it near at hand discerns it better at e than at f, especially as to the minute details."

In this passage Leonardo indicated his belief that accommodation is achieved by binocular convergence—and that loss of this function underlies the presbyopia of old age.

FIG. 5.

FIG. 6.

FIG. 5.—The correction of presbyopia with lenses. The glasses a, b, in front of the eyes c, d, are shown refracting light rays from images at e and f. (C.A.244.)

FIG. 6.—An early drawing of the eye, showing the optic nerve ending in the anterior of three ventricles represented according to mediæval ideas. To the left Leonardo compares the coats of the brain or eye, with the structure of an onion. Below, the lens is drawn, round and central in the eyeball—and an uncrossed course of the optic nerves. The auditory meati are also shown opening directly into the anterior cerebral ventricle. These drawings illustrate mediæval views, before Leonardo had dissected the parts himself. (Q.V.6v.)

Figs. 6, 7 and 8 are reproduced by gracious permission of H.M. The Queen.

The optic nerve, chiasma and optic tract are all illustrated by Leonardo. In early figures the optic nerve and auditory nerve are drawn ending in the anterior of the three cerebral ventricles, which he represents in a manner showing his early dependence on ideas probably derived from Albertus Magnus (Fig. 6).

Later he injected the cerebral ventricles with wax and obtained a more accurate idea of their shape and position. The optic chiasma is now clearly illustrated and the optic tract is drawn ending below the middle of the 3rd ventricle (Fig. 7).

Since the times of Posidonius about A.D. 300 the centre of sensation had been traditionally lodged in the anterior ventricle, to these accordingly Leonardo directs both the optic and auditory nerves in his early diagrams. Later he found that most of the sensory nerves appear to arise near the middle of 3rd ventricle and so he shifts the centre of sensation to this site.

The movements of the eye did not escape Leonardo's attention. "Why", he asks, "in

Fig. 7.—Drawings of the optic nerves, chiasma, and tracts, now shown passing to the base of the third or middle cerebral ventricle. The cerebral ventricles are now more accurately represented as a result of Leonardo's own wax casts of them. Comparison of these drawings with those in Fig. 6 reveals Leonardo's progress in anatomy. (Q.V.8r.)

turning the eyes, is one drawn after the other." (B.21r.) "Search for the motor nerves of the eyes, and consider if the principal ones are four or less, because in the infinite movements of the eyes four nerves do all, since as you leave the jurisdiction of one, aid comes from the second, and so it continues." (Q.IV.11.)

The results of his search are illustrated in a masterly drawing of the optic chiasma, the motor nerves of the eye and ophthalmic branch of the trigeminal nerve (Fig. 8). Galen and the anatomists of the Middle Ages recognized only the optic, oculomotor and ophthalmic division of the trigeminal as the nerves of the orbit.
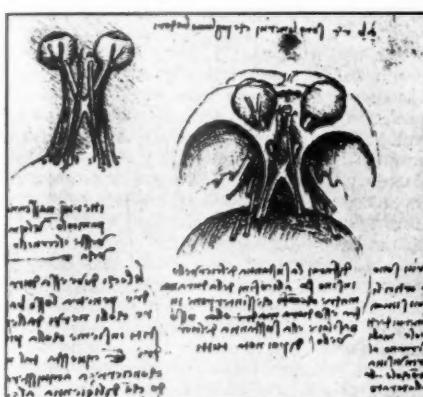
Fig. 8.—The nerves of the eye, and the optic chiasma. In this anatomical study the oculomotor nerve and ophthalmic division of the trigeminal are easily identifiable; the IV and VI cranial nerves are also shown. (An.B.35r.)

Leonardo concluded by suggesting that the optic chiasma is responsible for parallel movement of the eyes:

"Make an anatomical section of the head at the eyebrows, in order to find the cause of the equal movement of the eyes. This practically confirms that the cause lies in the intersection of the optic nerves." (C.A.305v.b.)

Stereoscopic vision was a particular concern of Leonardo the artist, who writes that the aim and design of a painter "is to manage a plane surface, so that on it may appear a body raised and standing out from the said plane. And he who in this point surpasses the rest, is the person to whom the palm of his profession is indisputably due." (Tr. of Painting p. 140.)

"Things seen with both eyes will seem rounder than those seen with one eye" he says (H.49r), in words descriptive of stereoscopic vision. Applying this rule to the difficulties of a painter he writes: "A painted figure must of necessity appear with less relief than a figure seen in a mirror (though both superficial) unless both be only viewed with a single eye"; the reason for which he explains at length by experiments described in the Treatise of Painting.

From his study of such factors he concludes:

"The figures of any body will appear loosened from the painting, and standing out with a great relief when the ground they are painted on is diversified with bright and dark colours" (Tr. of Painting p. 59).

Here, very briefly, is the basis from which he developed that chiaroscuro style of painting for which Leonardo is most renowned; it was a method built up from his knowledge of optics and designed to obtain a stereoscopic effect on a plane surface—it was the first attempt at 3D effects in painting.

Leonardo as a man of the Renaissance devoted intense study to the subject of perspective. "Perspective is a rational demonstration whereby experience confirms how all things transmit their images to the eye by pyramidal lines. Every bodily form as far as concerns the function of the eye is divided into three parts, namely substance, shape and colour. The image of the substance projects itself further from its source than its colour and shape, the colour also projects itself further than its shape.

"Experience shows that if you see a man near at hand you will be able to recognize the character of the substance, of the shape and even of the colour; but if he goes some distance away from you, you will no longer be able to recognize who he is because his shape will lack character; and if he goes still further away you will not be able to distinguish his colour,

but he will merely seem a dark body, and further away still he will seem a very small round dark body. He will appear round because distance diminishes the various parts so much as to leave nothing visible except the greater mass." (Ms. 2038 Bib. Nat. 12v.)

Perspective, "the bridle and rudder of painting", as Leonardo calls it, "is nothing but seeing an object behind a sheet of smooth transparent glass, on the surface of which everything behind the glass may be drawn; these things approach the point of the eye in pyramids; and these pyramids cut the said glass". (A.1v.)

Based on this definition he devised a practical method of drawing in perspective, described in detail in his Treatise of Painting, and illustrated in one of Albrecht Durer's woodcuts.

On a loose sheet in the Windsor Collection is a note of Leonardo entitled—"How the eye has no share in the creation of the colours of the rainbow". In it he describes how looking through a glass of water the colours of the rainbow may be seen. He is particularly concerned to show that this is not an optical illusion. "But if you place this glass full of water on the level of the window so that the sun's rays strike it on the opposite side, you will then see the aforesaid colours, producing themselves in the impression made by the solar rays which have penetrated through this glass of water, and terminated upon the floor in a dark place at the foot of the window: and since here the eye is not employed we clearly can say with certainty that these colours do not derive in any way from the eye." (Windsor Drawings 19150 r.)

Here he has anticipated Newton in producing the spectrum from white light. But Leonardo's own remarks show little approach to any colour theory. "White is not a colour in itself but only a faculty or disposition to receive colour; the blue of the sky arises from its being a dense transparent body illumined by the sun and placed between the earth and the darkness of the upper regions." "And this may be seen as I myself saw it, by anyone who ascends Monte Rosa a peak of the chain of the Alps." Thus for Leonardo the blue of the sky is a "compound colour" formed of white and black. "The medium that is between the eye and the object seen, transforms this object to its own colour. So the blueness of the atmosphere causes the distant mountains to appear blue: red glass causes anything that the eye sees through it to seem red." (Trivulzio 70a.)

Nevertheless Leonardo's observations were acknowledged by Goethe as vital to the development of his own Theory of Colours, and this still lives on in Hering's theory of colour vision in which opposite pairs of colours, including black and white, are fundamental.

Goethe's words to Eckermann on December 16, 1828, recall Leonardo's work on colour— "A short time ago I read in an English encyclopædia the doctrine of the origin of blue. First came the correct view of Leonardo da Vinci, but then followed as quietly as possible the error of Newton, coupled with remarks that this was to be adhered to because it was the view generally adopted. There is little new to be discovered or expressed", adds Goethe. "Even my theory of colour is not entirely new. Plato, Leonardo da Vinci and many other excellent men have before me found and expressed the same thing in a detached form; my merit is that I have found it also, I have said it again."

Leonardo himself found the eye, particularly the pupil, a miracle of Nature worthy of one of his few outbursts of admiration.

"It must be that the images of our hemisphere enter and pass, together with those of all the heavenly bodies through the natural point in which they merge and become united (the pupil of the eye) . . . whereby the image of the moon in the east and the image of the sun in the west at this natural point become united and blended together. . . . Who would believe that so small a space could contain the images of all the universe? O mighty process . . . what talent can avail to penetrate a nature such as this? What tongue will it be that can unfold so great a wonder? Truly none! This it is that guides human discourse to considering divine things; here the figures, here the colours, here all the images of every part of the universe are contracted to a point. O what point is so marvellous! (C.A.345v.b)

Abbreviations of References to Leonardo's manuscripts.

A, D, F, H, K. = MSS. in the Library of the Institut de France. An. A and B. = Dell Anatomia Fogli A and B. C.A. = Codex Atlanticus. Q. = Quaderni d'Anatomia, Vols. I–VI. MS. 2038 Bib.Nat. = MS. No. 2038 Italian MSS. Bibliothèque Nationale. Trivulzio = Codice Trivulzio.

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Section of Otology

President—JOSEPHINE COLLIER, F.R.C.S.

[*December* 3, 1954]

DISCUSSION: INTRACRANIAL THROMBOPHLEBITIS

Mr. E. J. Radley-Smith:

In 1951 it was written: "Those of us in practice soon after the First World War will have vivid memories of the severe cases of lateral sinus thrombosis with septicæmia and pyæmia, and huge extradural abscesses which were then a common occurrence. These have been gradually declining in frequency and since the advent of sulpha drugs and penicillin have become almost a rarity." It would be invidious for one who is not an otologist to confirm or contradict this statement and I have therefore referred to the figures published by one of your recent Presidents who in his Presidential Address reported on 1,379 personal mastoid operations. I find that in the period 1921 to 1936, before sulpha drugs, 3·5% of his mastoid operations were complicated by lateral sinus thrombosis; in the years 1937 to 1945 when he was using sulphonamides, the percentage fell to 2·5%; between 1946 and 1951 when using both sulphonamides and penicillin only 1% of his mastoid operations suffered this complication. Nevertheless this dangerous complication still occurs and in the last three years 8 cases occurred at the Royal National Throat, Nose and Ear Hospital.

Although it will be conceded, I think, that lateral sinus thrombosis is now decidedly less common, some other forms of intracranial thrombophlebitis are better understood and more widely diagnosed. Perhaps light has been thrown on these problems by the more frequent use of certain neurosurgical investigations and in carotid arteriography we have a positive method of diagnosis in some instances.

Cavernous sinus thrombosis is a condition which is perhaps more frequently diagnosed than the facts would appear to merit. Cavernous sinus thrombosis, serious though it still undoubtedly is, carries to-day a very different prognosis from that of the late 1920s. I shall not easily forget, as a student memory, the autopsy of the sister of one of my own medical student friends who died of this condition within a few days of developing a carbuncle on the upper lip. That was then the all too frequent outcome of cavernous sinus thrombosis. To-day the ætiological conditions are the same—my last 2 cases followed a boil in the nose and tonsillitis—but the outcome is usually full recovery when energetic and, above all, early treatment with the appropriate antibiotic is used. In addition to that treatment I have a great regard for short-wave diathermy in this and other deep infections for surely it is the one form of counter-irritation which does penetrate deeply. On the other hand I am rather afraid of the anticoagulants in any form of obviously infective thrombosis for the drugs may hinder the formation of thrombosis which is the natural barrier against still further spread of infection in the vascular system. In addition to this danger, Kendall refers to the special risk in puerperal cases of intracranial thrombosis and mentions two severe uterine hæmorrhages occurring during the use of anticoagulants in the treatment of superior longitudinal sinus thrombosis. In all intracranial thrombophlebitis prolonged medication with anticonvulsants is most wise but often overlooked!

Are the serious intracranial complications of mastoid surgery, of which intracranial thrombophlebitis is one, really decreasing parallel with the great decline in acute mastoid surgery? Again, an analysis of Archer's figures (Table I) suggests that some at least of the infective complications are still, proportionately, common.

TABLE I.—SHOWING MAIN COMPLICATIONS IN 1,379 MASTOID OPERATIONS (Archer, 1952)

	Labyrinthitis cases	Brain abscess cases	Lateral sinus thrombosis cases		Mastoid operations
1921–1936	59 7·7%	20 2·6%	27 3·5%	in	767
1937–1945	52 12·7%	5 1·2%	10 2·5%	in	409
1946–1951	46 22·6%	6 3%	2 1%	in	203

Thus although the florid lateral sinus thrombosis is considerably less common, brain

V* MAY

abscess appears to be at least as common. I believe that many brain abscesses are the end-result of thrombophlebitis. Temporosphenoidal and cerebellar abscesses of otitic origin are not always up to the surface of the brain and these rather deeper abscesses I conceive to have resulted from infective thrombosis extending in from the cortical vessels.

In a very general neurosurgical practice 15 of my last 29 brain abscesses came from infections of the ear or nose.

Otitic hydrocephalus is an interesting form of cranial thrombophlebitis. In this condition the ventricles are not dilated during life as shown by ventriculography, nor is there any excess of subarachnoid fluid. There is, therefore, neither external nor internal hydrocephalus. Whenever I have performed ventriculography in these cases I have been impressed with the difficulty in finding the lateral ventricles, as if they were squashed by an œdematous brain. Indeed I think they are, in fact, compressed and diminished by cerebral œdema resulting from venous obstruction in all acute stages of the condition. Probably the ventricles are only dilated in the very late stages of protracted trouble in which some degree of cerebral atrophy, local or general, may eventually have occurred.

The clinical picture of otitic hydrocephalus should be kept in the forefront of our diagnostic minds for the syndrome may not be as clear cut as, for example, that of a brain abscess in the presence of cholesteatomatous erosion. The intracranial thrombotic process may commence insidiously at a time when the ear is not particularly active. Furthermore, when it is traversing a so-called "silent area" of the brain, its symptoms may be far from characteristic. The infective process may creep slowly and even intermittently from a symptomatic point of view, across the wide expanses of the hemispherical cortex so that it reaches the superior sinus at a date when the ear condition may well appear quiescent. The late development of symptoms is illustrated by the length of the interval between active ear infection and the onset of high intracranial pressure which varies between 4 and 100 days—in a recent case of my own the interval was 38 days! The headaches therefore develop when the ear infection is a little in mind. This is a diagnostic catch, which is illustrated by the fact that a case of otitic hydrocephalus which I saw last year had been admitted to the fever wards labelled "? enteric fever"—no complaint having been made by the patient of her ear. I have tabulated the characteristic clinical picture and investigations of otitic hydrocephalus thus:

Causal Infection
   Ear. Often chronic and comparatively quiescent when symptoms of otitic hydrocephalus begin.
   Nose. "Cold" with perhaps frontal sinusitis. "Influenza" with no definite ear, nose or throat infection.
   Distant Infection. Recent case from infected bunion.

Symptoms
   Severe headache, vomiting, drowsiness and all intervening stages to coma, vertigo, papilloedema, neck stiffness, fits, i.e. intracranial pressure symptoms.

Evidence of Infective Disease
   Often slight; perhaps no pyrexia; pulse not raised as in infection but bradycardia of high intracranial pressure.

Cerebrospinal Fluid
   Pressure very high, $300++$. Content normal—no cells. Chemically normal. Pressure markedly reduced by removal of small quantities of cerebrospinal fluid.

Ventriculography
   Ventricles small or normal. Not displaced or distorted locally.

Other Investigations
   Electroencephalogram—diffuse abnormality. Phlebogram may show thrombosis of the superior longitudinal sinus.

Otitic hydrocephalus should be treated energetically as cure is often possible. The process is initially infective and therefore thorough medication with antibiotics should be started as soon as possible. This is not only valuable in direct treatment of the thrombophlebitis but also to provide some protection against spread of systemic infection when the original infective focus is treated surgically wherever applicable. I do feel very strongly that this should be done at an early stage. Not to do so seems rather like treating a peritonitis of appendicular origin without removing the vermiform appendix. Important though antibiotics and eradication of the septic focus undoubtedly are we must remember that the immediate precipitating cause of symptoms is the high intracranial pressure consequent upon thrombosis of the superior longitudinal sinus. Venous engorgement must provide a material contribution to this high intracranial pressure for eight superior cerebral veins on

each side usually drain into the infero-lateral aspect of the sinus. Furthermore, reabsorption of the cerebrospinal fluid back into the venous system chiefly occurs in the lateral lacunæ of the superior longitudinal sinus. These are the reasons for such high intracranial pressure when the superior sinus thromboses! This must be relieved or sight, and even life, will be threatened. Lumbar puncture, if repeated often enough, is, I consider, still the stand-by of treatment in this respect. Repeated lumbar punctures tide the patient over the period of excessively high pressure while the processes of natural accommodation and therefore cure can proceed by re-canalizing the sinus itself and by opening up other anastomotic venous channels. At first lumbar puncture may be required twice a day. The interval between taps is later lengthened according to the level of pressure recorded at each one. This treatment is irksome to the patient and staff but both have their reward in the almost instantaneous relief of headaches and increased alertness of the patient following each tap. When burr holes have been made in the skull the ventricles may be tapped and a like effect obtained. It seems pretty certain, however, that many cases of otitic hydrocephalus will continue to be treated where the resident medical staff do not feel confident in tapping ventricles.

The mortality rate in otitic hydrocephalus is considerable for reasons which are only too apparent when the pathology is considered. The very high intracranial pressure found in this condition is intrinsically dangerous as also is its relief, whether by lumbar puncture or, to a lesser extent, by ventricular tap. Repeated invasion of the subarachnoid or ventricular spaces by the needle is not without hazard and certainly makes great demand on the fortitude of the patient no less than upon the skill and devotion of the resident medical staff. The thrombotic process may spread widely and if it is decided to use anticoagulants further dangers are added. Kendall (1948) in a recent survey suggests a mortality of 30% even in puerperal cases in which we are not faced with intracranial infection. If the mortality is to be reduced we have to look towards even further, and earlier, co-operation between the otologist, the neurologist and the neurosurgeon.

It is convenient, but frequently somewhat inaccurate, to fit the label of a well-recognized diagnosis to a patient's illness. Often the disease lies, as it were, between two or more diagnoses. Otitic hydrocephalus may be the very late result of a chronic ear infection, occurring many weeks after the most recent exacerbation. I visualise that the latent interval is occupied by a creeping thrombosis of the intervening cortical veins. This brings me to a consideration of "cortical thrombophlebitis" which may be the link between the ear and the superior sinus thrombosis. Cortical thrombophlebitis may never reach the superior sinus. Either may occur without the other and doubtless people suffer from both at the same time which so inconveniently upsets our cherished "typical picture"!

Cortical thrombophlebitis, is, I fancy, not a very rare condition and is encountered in several branches of medicine, but perhaps especially in otology and neurology, for the process often starts in infections of the ear and paranasal sinuses. The process may spread for a time and then resolve; it may reach a major dural sinus; it may produce a cerebral abscess. It exists sufficiently often in its pure form to make some understanding of it becoming in an otologist.

The causal infection may be an acute otitis media, a "sore throat", an infected bunion, a septic abortion, to quote 4 recent cases.

Epileptic fits, both early and persistent, are prominent symptoms of the condition. So cortical a lesion may well be expected to cause fits. Fits are, I feel, much more frequent in, and characteristic of, cerebral thrombophlebitis than the deeper, more medullary, cerebral abscess. Headache is less prominent than in abscess because in quite a few instances the intracranial pressure is not raised in thrombophlebitis. Tingling in a part of the body may be present for two or three weeks, perhaps fluctuating in area, before any other symptoms arise.

The neurological signs sometimes indicate a very extensive cerebral involvement, i.e. both motor defect and cortical sensory loss. Pressure is sometimes but little raised for there is no space-occupying lesion and the superior sinus may never become thrombosed to add the factor of defective absorption of cerebrospinal fluid. Lumbar puncture shows an increase in the white blood cells in the cerebrospinal fluid; the total is often less than 100, which would be consistent also with a well-encapsulated abscess. The differentiation between these two conditions may be aided by a plain, but very accurately centred, antero-posterior X-ray of the skull, for if the pineal gland is calcified it will usually show a discernible displacement in the presence of an abscess but none in thrombophlebitis. I regard this as a very useful first investigation for it can be done in almost every hospital and is both safe and painless. Ventriculography and arteriography give a normal picture. Occasionally circumstances arise which incline one to make exploratory burr holes and this has, in a few instances, demonstrated a macroscopically normal cortex in one area and a waxy, yellowish appearance in another, indicating some vascular damage. The differential diagnosis is, of course, cerebral abscess and it is important to decide which is, in fact, present

as thrombophlebitis needs no definitive surgical treatment whereas the abscess does require it at the appropriate stage of encapsulation.

Treatment is by intensive chemotherapy and antibiotics. Failure to cure arouses the suspicion of abscess. Control of the fits may be a major problem and status epilepticus is not rare. After the condition is cured very prolonged medication with phenobarbitone is necessary. Vascular softening of areas of the brain may follow but apparently complete cure often results.

Thrombosis of the superior longitudinal sinus is well known in the absence of any intra-cranial or paracranial infection. I should like to refer briefly to just two such examples:

A. Superior sinus thrombosis has long been recognized in the puerperium. Ménière (1828), Churchill (1854), Collier (1891), Gowers (1893), all described intracranial thrombosis after childbirth, and the infrequent autopsies sometimes demonstrated the thrombosed superior sinus. Interest in this type of so-called "primary thrombosis" has been revived in the last two decades by the papers of Symonds (1937, 1940, 1944) and Martin (1941, 1944) and much debate has raged as to whether the intracranial thrombosis is truly primary or whether it is embolic, perhaps via the vertebral venous plexus, from pelvic thrombosis. Some examples appear to be aseptic and primary but all gradations occur up to the obviously septic intracranial thrombosis complicating septic abortion. In the puerperium certain factors arise which predispose to superior sinus thrombosis. The intermittent severe straining during labour with high intra-abdominal and intrathoracic pressure must cause waves of very high intracranial venous pressure during which damage to the vascular endo-thelium may occur, forming a point of origin for clotting. If at that time the blood is "sticky" as Wright (1942) has shown it to be in the puerperium or if there is any infection in the body, the thrombosis may spread in clinical proportions.

B. A somewhat similar process has been observed during treatment of the mentally afflicted by insulin therapy. Convulsions are, of course, frequently caused during this treatment which may well injure the endothelium of the intracranial sinuses. Blood-vessel damage, especially shown in the intima, has frequently been shown post mortem in insulin therapy (Ferraro, Jervis, Kastem). Clotting on the damaged endothelium may be assisted by alteration in the circulating blood for the hypoglycæmic coma which is the desired result of insulin therapy is usually accompanied by profuse sweating. Since 30 to 50 treatments are administered the patient is exposed to these factors for long periods. I was able to observe 3 cases of superior sinus thrombosis arising during insulin therapy in one mental hospital within a period of six months.

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Mr. Norman Crabtree:

The following is an account of cases of intracranial sinus thrombophlebitis which have arisen as a result of otitic suppuration. The condition has been profoundly modified since the introduction of the sulphonamides.

I have reviewed the cases of otitic infection undergoing mastoid surgery in two four-year periods since 1941 under two headings; those having cortical, and those having radical or modified radical procedures, to differentiate the acute and chronic case.

The first is 1941 to 1945 (Table I). Although penicillin was used in the treatment of some

TABLE I.—1941–1945

CORTICAL 115			RADICAL 31			
Intracranial complications						
Thrombophlebitis	..	2	Perisinus abscess, cerebellar			
Perisinus abscess, one probably			abscess	..	..	1 Died
thrombosed ..	..	2	Cerebral abscess	..	..	1 Died
Meningitis	..	1	Meningitis	..	..	1 Died

of the later cases, it was not administered before the diagnosis was made. The records of 146 cases are available, 115 cortical and 31 radical. The intracranial complications arising

in the acute cases were: thrombophlebitis 2, perisinus abscess 2—one of which developed temporary post-operative tenderness in the neck and was probably a case of thrombosis—and meningitis 1. In the chronic cases, the 3 complications were all fatal: a perisinus abscess associated with a cerebellar abscess, a meningitis and a cerebral abscess.

My second period is 1950 to 1953 (Table II).

TABLE II.—CORTICAL MASTOID OPERATIONS 1950–1953

Bilateral without complications	15
Cortical without complications	104
Complications	
Lateral sinus thrombosis 4	
Perisinus extradural 3	
Facial paralysis 1	
Cerebral abscess.. 1	
Cerebellar abscess 1	
Total complications..	10
Total operations	144

These cases are representative, though the incidence of intracranial complications has been weighted by our association with the Neurosurgical Unit. Taking the 144 cortical operations first, 15 were bilateral and free from complications. 10 of the 114 unilateral cases were complicated, lateral sinus thrombosis being the most common with 4 cases, against one each of cerebral and cerebellar abscess.

Turning to the radical procedures we find (Table III) that there were 54 complications in

TABLE III.—RADICAL AND MODIFIED RADICAL MASTOIDECTOMY 1950–1953

	No complications	Complications	Total
No cholesteatoma ..	101	11	112
Cholesteatoma ..	54	43	97
Total	155	54	209

209 cases, under 10% where the presence of cholesteatoma was not recorded, but in nearly half those with cholesteatoma.

A detailed analysis (Table IV) shows circumscribed labyrinthitis in 16, and exposure of

TABLE IV

Cholesteatoma with complications		*Complications without cholesteatoma*	
Fistula lateral semicircular canal	16	Perisinus abscess	2
Facial nerve exposed without injury ..	4	Extradural abscess	3
Facial paralysis with recovery	2	Posterior fossa subdural abscess..	1
Facial paralysis without recovery ..	3	Cortical venous thrombosis ..	1
Cerebral abscess	5	Lateral sinus thrombosis	2
Cerebellar abscess (one with facial paralysis)	3	Hysterical paraplegia	1
Acute labyrinthitis	2	Cerebral abscess	1
Acute labyrinthitis, meningitis	2		
Invasion of internal ear	2		
Meningitis	2		
Meningitis, ventriculitis	1		
Lateral sinus thrombosis	1		

the facial nerve in 10, while of the intracranial complications there were 9 brain abscesses (5, 3 and 1), against 3 of lateral sinus thrombosis (1 and 2).

The incidence of thrombosis in this second series of cases (Table V) is 2% of the total and 11% of all complications.

TABLE V.—INCIDENCE OF THROMBOPHLEBITIS

	Cortical	Radical	Total	Percentage
Sinus thrombophlebitis ..	4	3	7	2
Perisinus abscess	3	2	5	1·4
Brain abscesses	2	8	10	2·8
Exposure of facial nerve, with				
and without paralysis ..	1	9	10	2·8
Total complications.. ..	10	54	64	18·1
Total operations	144	209	353	

Sinus thrombophlebitis = 11% of all complications.

5 of our cases died (Table VI), 2 of brain abscess and 1 of sinus thrombosis in which a cerebellar abscess later developed, out of the 7 cases.

TABLE VI					
Deaths following cortical mastoidectomy					
Cerebral abscess	..	..	..	..	1
Cerebellar abscess	..	..	..	..	1
Deaths following radical mastoidectomy					
Posterior fossa subdural abscess, leptomeningitis				..	1
Lateral sinus thrombosis	..	..	..	..	1
Glomerulonephritis (incidental)	..	..	..	1
Sinus thrombophlebitis: 1 died out of 7					
Brain abscess: 2 died out of 9					

TABLE VII.—TEN YEARS 1926–1935	
Cavernous sinus involved	.. 1
Cortical operation	.. 9
Evacuation thrombus	.. 7
Ligation I.J.V.	.. 8
Results	
Recovered ..	 5
Died	 5
Transferred with diphtheria	1

We have, therefore, 4 cases occurring in acute and 3 in chronic mastoiditis, and in fact over the past ten years we have had an equal incidence, 8 of each.

How do these findings compare with those before sulphonamides? I have no personal experience, but one of my senior colleagues has kindly let me study his hospital records over the ten years 1926 to 1935 (Table VII), during which time he personally had 11 cases, all acute or subacute, all under 17 years of age. In 1, the cavernous sinus was also involved. This child and an infant died without operation. In the other 9 the mastoid was opened, thrombus evacuated in 7 and internal jugular vein ligated in 8. 5 cases recovered, 5 died and 1 was apparently recovering when it developed diphtheria.

Comparing the three series, and allowing for local circumstances, a general broad inference may be made that the total incidence of sinus thrombophlebitis has fallen to about a quarter since 1935. The incidence in acute mastoiditis has been virtually decimated in proportion with the reduced incidence of mastoiditis, and a previous mortality rate of 50% almost eliminated.

On the other hand, there is now an equal incidence of thrombophlebitis complicating acute exacerbations of chronic mastoiditis, and this is still a dangerous condition, and it looks rather as if there may be an absolute increase in these cases.

CLINICAL FEATURES

Our clinical material consists of 16 cases of sinus thrombosis which have been admitted since 1943, 8 in acute cases and 8 in chronic.

Only 2, both acute, occurred before penicillin was generally available. There was an additional acute case which never reached the otologists, a baby 8 weeks old who died within a few hours of admission after three days' enteritis. Post-mortem examination showed the right mastoid cells full of pus and the lateral sinus distended with thrombus extending $\frac{1}{2}$ in. into the sigmoid sinus and backwards into the superior longitudinal sinus.

6 of the 8 acute cases were admitted as mastoiditis, the remaining 2 with embolic complications, an empyema and a pyarthrosis of the left knee.

The empyema was in a girl aged 6 in 1945 who had had an attack of otitis media three months earlier.

She improved following aspiration, a week later developing earache with a spiky rise of temperature over a further week, despite sulphadiazine. At mastoidectomy a thrombus was removed from 1 in. along the transverse sinus to the jugular bulb. Free bleeding was not obtained here and the internal jugular vein was ligated and pus drained from the upper end. She was apyrexial the following day and her further progress was uneventful.

The other case was a boy, aged 6 when admitted in 1948, two weeks after an attack of otitis, with a rigor followed a day later by pyarthrosis of the left knee. Rigors continued and led to the disclosure of a mastoiditis four days later. The thrombosed sinus was not opened at operation, but he had no post-operative symptoms.

There were no acute cases over 12 years of age, while ages in the chronic cases ranged from 20 to 52. Earache had been present in most of the acute cases for two or three weeks, but in all but one the membrane was intact.

5 of the 8 chronic cases were admitted as mastoiditis, and 1 of these subsequently died of cerebellar abscess. The remaining 3 were neurosurgical admissions—a cerebellar abscess which subsequently died, a temporal lobe abscess which recovered, and a persistent parietal headache and low-grade fever without any aural history. The parietal headache took several weeks to resolve after mastoidectomy without opening the sinus, encephalography showing a diffuse abnormality in the right temporal lobe.

In the other cases the history of discharge varied from six months to thirty years, with pain and increase of discharge, usually foul, from three to ten days before admission, so these exacerbations progressed more rapidly than the acute cases.

Chemotherapy in considerable dosage had been administered to at least 10 of the cases

before admission, but whereas most of the acute cases had sulphonamides (and none had penicillin), most of the chronic cases had penicillin as well.

Rigors occurred in the 4 earliest acute cases, and in 1 recent chronic case which had penicillin only. In 3 of these acute cases, a spiky rise of temperature of the classical type was seen, while in a further acute case the temperature swung at a high level for a week following myringotomy, despite the combined administration of penicillin and chloromycetin. There was a dramatic restoration of normal temperature after mastoidectomy and evacuation of the clot.

In 1950 Brownlie Smith drew attention to the importance of the temperature chart in the diagnosis of thrombophlebitis. In several of our cases a persistent elevation of temperature was again the cardinal sign and in 5 the only sign, while even this was absent in one case. Parietal headaches were the only additional symptom in 2 other cases, while definite symptoms and signs of meningeal irritation or brain involvement, drowsiness or irritability with neck rigidity and a positive Kernig's sign, were present in varying degree in 6 cases.

INVESTIGATIONS

Throughout the series, there is a general failure of positive identification of the causative organism.

There were bacteriological examinations in all but 2 cases. Beta hæmolytic streptococci were present at myringotomy in the pyarthrosis case, which had no previous chemotherapy. A scanty growth was found in the mastoid of an acute case where earache and low-grade fever recurred three weeks after an acute otitis without otorrhœa. Again, though the original otitis was treated with sulphonamides, he had none during the two weeks before operation. In all other cases culture was either sterile or grew contaminants only.

We rarely see these complications in cases admitted early enough to obtain positive cultures and antibiotic sensitivities, since we are led by these tests to use a wide variety of antibiotics, either alone or in combination. I believe that the incidence of complications such as sinus thrombosis at the present moment is more due to the persistence with treatment of mastoid infection by an unsuitable antibiotic without initial myringotomy and culture than to the type or virulence of the causative organism.

The dramatic response to surgical drainage in some of those cases showing high swinging temperature demonstrates a localization of infection presumably by the chemotherapy to the limits of the surgical field exposed.

I should like to compare this with a pre-sulphonamide case, a boy of 12, in 1934.

Here the temperature continued to swing with rigors for a week following evacuation of the clot and ligation of the internal jugular vein. The administration of antistreptococcal serum was followed by an immediate resolution of the fever.

In earlier days, importance was attached to the presence of a leucocytosis, but this was only present in 2 of the 5 acute cases in which it was investigated, 1 being the pyarthrosis.

Of the chronic cases, 2 with brain abscesses had a leucocytosis of 17,000. In a further case, a count of 14,600 was the only finding other than earache and a low-grade fever.

It is evident, therefore, that the presence of a leucocytosis may sometimes be of value in diagnosis, while no significance can be attached to its absence.

Lumbar puncture was only performed pre-operatively in 2 cases who also had brain abscesses, and in a man of 37 who had intermittent discharge following a cortical mastoid-ectomy fifteen years previously. The ear ceased to discharge ten days before admission, with an increasingly severe headache and giddiness, and temperature rising to 103° F., despite the administration of penicillin and sulphadiazine. He was confused on admission with a partial upper motor neurone facial paralysis, marked neck rigidity and a positive Kernig's sign. His lumbar puncture showed a marked increase in pressure, and at operation a large cholesteatoma and perisinus abscess were found. The sigmoid sinus was thrombosed but not opened. His drowsiness rapidly cleared and his temperature remained normal until the thirteenth day, when he had a small pulmonary embolus which settled rapidly with penicillin and sulphadiazine.

Cultures of the cerebrospinal fluid were negative, and in the only case in which blood culture was undertaken, this was also negative. In view of the difficulty of identifying organisms in the wound itself, it is doubtful whether these procedures are of any present value.

There is a manifest lack of confidence in the value of jugular compression tests during lumbar puncture, and where applied its validity is open to question. Its use has only been recorded in one case before operation, and post-operatively in another. On both occasions a free rise was recorded.

The difficulty in assessing this test has long been recognized, and in 1942 Freedman and Melton drew attention to errors arising from the Tobey-Ayer test (1925), due to a failure to appreciate the common anatomical variations and the underlying physiological principles.

They described a modified test in which the suspected side was placed lowermost. Their two positive criteria are that the response from the lower vein should be nil or less than 20 mm. of pressure change, and that from the upper vein should be equal or nearly equal to that produced by bilateral compression. This can be decided by compressing both veins and then releasing the lower.

Some of our cases show that delay in operation may not necessarily be fatal or even serious, but I feel that a more frequent and knowledgeable use of this test would have saved much morbidity by aiding an earlier diagnosis.

Where recorded, the acute cases showed cellular mastoids.

Most of the chronic cases were of course sclerotic, but one in a patient with thirty years' otorrhœa, showed long-standing infection in a cellular mastoid (Figs. 1 and 2). There is a translucency in the antral region which was reported as a possible cholesteatoma (Fig. 2).

Fig. 1.—Normal side, showing well-pneumatized cell system.

Fig. 2.—Infected side, showing extensive mastoiditis, with area of translucency over the genu of the laternal sinus, corresponding to the erosion of the sinus plate.

At operation there was necrosis and a large foul-smelling perisinus abscess with a slough overlying an exposed and thrombosed sinus. The sinus was not opened.

OPERATIVE FINDINGS

Findings at operation varied from a little pus in the mastoid process to gross necrosis with pus under pressure. Cholesteatoma was present in only 2 of the chronic cases.

In 9 cases in which a perisinus abscess was present, granulation tissue on the sinus dura was rarely noted. This is in contrast to the massive granulations which are usually found in this region in cases of perisinus abscess without thrombosis. The appearance of the sinus wall varied from a slight to marked thickening and complete lack of resilience, and varied in colour from white or yellow to dark blue or black.

In all cases, thrombosis appeared to be due to direct spread of infection from the mastoid. Transmitted intracranial pulsation was usually present. Where the extent of the thrombosis was explored, relatively small thrombi were in the upper sigmoid sinus, the more extensive extending up to 8 cm. along the transverse sinus, and in 2 cases down to and including the jugular bulb. One contained an intrasinus abscess.

In the case of pyarthrosis of the knee, a large perisinus abscess was found compressing and obliterating the lumen. On evacuation of the abscess, the sinus was found slowly to fill up and was not opened. It was clear from the previous history that a thrombophlebitis was present.

In cases where the condition of the petrosal sinuses and the mastoid emissary vein were noted, they were found to be patent, and we have, in fact, no evidence that in any of our cases did the thrombus extend beyond the confines of the lateral sinus and the jugular bulb, except in 1 certain and 1 doubtful case of involvement of the internal jugular vein at the upper end.

DISCUSSION OF OPERATION

We have no evidence of involvement of other venous sinuses through pathways described in the past—such as spread to the superior sagittal or the opposite lateral sinus via the toreula, the occipital sinus to the vertebral plexus, the petrosal sinuses to the cavernous sinus, the mastoid emissary vein to the occipital vein, or through the common facial vein and the pterygoid plexus and so again to the cavernous sinus.

There are, however, 2 cases where there was probably an associated cortical venous thrombosis.

In view of the minimal signs and symptoms often present, we must accept that incipient or actual thrombosis may nowadays often occur during mastoiditis without producing recognized clinical symptoms. If this can occur, it is equally true with regard to spread of the thrombosis into the other sinuses.

It will be seen that in none of our cases since the introduction of penicillin has the internal jugular vein been ligated. The wisdom of this procedure was in doubt in earlier days. Körner produced statistics in 1925 which showed no difference between the results obtained with and without ligation, and Grünberg, reviewing the figures of 11 authors was unable to draw any definite conclusions.

The objection to jugular ligation is that while only shutting off the main highway, the disturbance of flow may invite dissemination through other channels. Ligation does not always bring security since infected thrombus may form proximally to the obliteration. One of my colleagues has recounted a presulphonamide case of his where this occurred, even after two ligations, and the infection was only controlled with recovery of the patient by ligation of the innominate vein.

The present evidence is that there can be little need for ligation at the time of mastoidectomy, even should the upper part of the vein itself be thrombosed, but should such a thrombus continue to extend, it would be wise to ligate before it reaches the common facial vein. Spread is favoured by venous stagnation and there is therefore a tendency for it to be arrested at a point of inflow. Should this point be passed, conditions favour more rapid spread.

The question as to whether the thrombosed sinus should be opened and the clot evacuated, or left alone after clearance of the surrounding disease, is the major decision which now faces us in the surgery of every case. In 10 of our cases the sinus was opened and in 6 unopened. The operation records show clearly that the line of action taken depended on the eight surgeons carrying out the operations and bore no relation to the state of the sinus and surrounding structures, or to the clinical condition of the patient. The subsequent progress is therefore of particular interest, and apart from the two fatalities, was remarkably uneventful.

The 6 acute cases in which the clot was completely removed, and the 2 acute cases which were not opened, recovered without further complications.

Of the chronic cases, the sinus was opened in 4 and left unopened in 4. The results of the opened cases were:

(1) No post-operative symptoms.

(2) Pre-operative meningeal signs, none post-operatively.

(3) Persistence of pre-operative parietal headache for some weeks due to cortical venous thrombosis.

(4) A cerebellar abscess which died. This was the case where the intrasinus abscess was found. She was aged 38 on admission in 1950, and had had bilateral intermittent otorrhœa for many years, the left ear having dried for several months.

Two weeks before admission she had malaise and left-sided headaches with increasing neck rigidity. Sulphathiazole a week before gave temporary control of her pyrexia, but when this was changed to penicillin because of vomiting, there was a return of pyrexia up to 104°. She showed mastoid tenderness and a copious foul purulent discharge with a sagging posterior wall. The only abnormal neurological sign was a mild low-grade papillœdema, and lumbar puncture showed slightly raised cells and protein. Operation showed a sclerotic mastoid with extensive necrosis of the sigmoid sinus. There was a great deal of white liquid pus in the perisinus region and pus of the same consistency was found under pressure inside the sinus. A small catheter was passed 8 cm. backwards along the transverse sinus until it met obstruction, and then downwards to the jugular bulb. A ventriculogram was negative, and the neurosurgeons considered that her papillœdema and headaches were related to the sinus thrombosis, possibly with associated cortical venous thrombosis. Her ear healed completely and she was discharged symptom free.

Her subsequent progress is a tragedy. A week later she was perfectly well but her ear was seen to be discharging a little pus, the significance of which was not apparently realized. In five days she developed drowsiness and an occipital headache, two days later was admitted as an emergency with extreme cerebral irritation, and died within a few hours. At post-mortem the transverse sinus was normal, the lower part of the sigmoid sinus was necrotic and there was a small collection of extradural pus in communication with an extensive abscess of the lateral lobe of the cerebellum.

The aspiration of the abscess may have disturbed the thrombus at the lower end, broken down tissue barriers and led to or aggravated the cerebellar abscess. A simple incision and drainage of the intrasinus abscess might have been wiser, and in full accord with general surgical principles. This case illustrates that if a clot is to be evacuated, removal must be complete. The possibility of thrombophlebitis arising again at each end of the obliteration must also be taken into account.

The results of the unopened cases were:

2 cases without symptoms. One of these was a temporal lobe abscess following chronic mastoiditis which failed to improve despite repeated aspirations, and in two weeks developed a contralateral hemiparesis and a more generalized headache attributed to a cortical venous thrombosis. When operation was undertaken, a solid lateral sinus with an extradural abscess were found but the sinus was not opened, and her symptoms cleared rapidly. Regarding this and one or two other similar cases, our neurosurgeons have since said that a lack of full appreciation of the mastoid pathology led them to counsel an undue delay of mastoid operation because of an unfavourable response of the intracranial lesion.

The third unopened case had the minor pulmonary complication two weeks later, and the fourth was the other fatal cerebellar abscess case. She was our oldest case, 52 in 1946, admitted with a history of ten days' vomiting and increased foul otorrhœa. She was drowsy on admission, with a normal temperature and a contralateral extensor plantar response. Lumbar puncture was normal. A large cholesteatoma with extensive bone destruction was found at operation, together with a foul-smelling extradural abscess. Her condition steadily deteriorated and she died five days later. Her brain showed some congestion over the temporo-sphenoidal lobe with a localized abscess in the cortex of the cerebellar hemisphere corresponding with the extradural abscess, and there was a small ante-mortem thrombus in the sinus. The significance of the thrombosis is doubtful, as it may have been terminal.

CONCLUSION

The results of treatment of lateral sinus thrombosis show that there is little to choose at the moment between opening the sinus and leaving it alone, and certainly no dogmatic preference for either procedure is justified.

In earlier days brain abscesses were explored through the infected mastoid wound. We never dream of doing this now, any intracranial exploration being through an independent clean field.

It would be another step forward if we could limit ourselves in the treatment of lateral sinus thrombosis to a meticulous clearance of extradural disease, except perhaps for incision of a rare intrasinus abscess.

Our few cases do not show any objection to this procedure, but to do it with confidence would require the assurance of full antibiotic control of the causative organism.

In only 2 of our cases was this possible, because in the other cases chemo- and antibiotherapy preceded bacteriological examination.

This shows again what has so frequently been said and is more frequently neglected, that bacterial culture should be initiated before therapy, and this is particularly important in acute exacerbations of chronic mastoiditis.

I should like to thank my colleagues, Mr. W. Stirk Adams, Mr. A. J. Moffett, Mr. R. R. S. Strang, for permission to review their records, and the many people of the staff of the United Birmingham Hospitals for their willing help and co-operation, in particular my Registrar, Mr. G. Dalton.

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Mr. Ian Robin, in opening the discussion, said that one point which had been brought home to otologists seemed to be the need for stressing to their students and house surgeons that their specialty was integrated with other branches of medicine. He could not help feeling that otologists should spend much more time on ætiology and a study of the actual process in which the condition occurred. One point was whether surgeons were wise in exposing the dura during operation for a very badly infected mastoid. He would not expose it unnecessarily. Another point was whether at operation surgeons did not tend to be rather heavy-handed.

His impression was that the condition was more common in young adults. He could recall 3 cases in particular. American literature stressed the danger of over-dosage of penicillin; some writers said that penicillin actually encouraged thrombus formation. The smaller the dose the less harm apparently it did. Some of the organisms might be anaerobic rather than aerobic. Perhaps their pathological colleagues might be asked to give them their findings. He had been interested to hear of the danger of heparin. One of the openers had mentioned the superior petrosal sinus. When this sinus was involved, the diagnostic signs were facial neuralgia and lower jaw toothache.

It was important to stress the need for observing early signs and symptoms, such as recurring headaches, and the necessity for neurological investigation. Minor neurological findings should be recognized and the offending focus discovered. They often learned about these diagnostic signs and symptoms from the patient's relatives, and an opportunity of questioning them should not be wasted.

Mr. Francis McGuckin: Two colour-slides of a case of cavernous sinus thrombosis were shown. The patient recovered on medical and nursing treatment only.

In the study of otogenic intracranial disease three clinical pictures emerge.

In brain abscess the dominant feature is pressure, a head containing more than it ought to; in thrombophlebitis it is sepsis: a wide fluid-system invasion; in meningitis it is sepsis plus pressure: a fluid-system sepsis in a head containing more than it ought to. The coming of modern medical remedies has not greatly altered this approach and I still think that a good history and wideawake observation may eliminate that shameful word "masking", which like the entity of post-operative lateral sinus thrombosis has something of excuse but little of reason.

(1) (*a*) The typical chart in brain abscess shows low or subnormal temperature with a pulse of 40–80. This is pressure.

(*b*) The typical chart in thrombophlebitis shows high peaks with a pulse of 100 or very much higher. This is sepsis.

(*c*) The typical chart in meningitis is half-way between these two with a pulse of 80–100. This is sepsis plus pressure.

To summarize—a good history and simple information about temperature and pulse will provide a shrewd idea of the complication.

(2) To wait for rigors before diagnosis of lateral sinus thrombosis is to wait until the protective process has failed. The disease should be suspected rather than diagnosed and nowadays it may sometimes be managed entirely by medical measures. This statement is not made lightly. It is based on an immense mass of material. In the Royal Victoria Infirmary we have seen since 1928 not less than 177 cases in which lateral sinus thrombosis was proved to be the principal complication.

(3) The more complex and ingenious tests for sinus thrombosis depend on complete

obstruction and they fail if the involved sinus is small.   They cannot help in mural thrombosis —neither can needling.

(4) The two lateral sinuses may differ greatly in size.   In this event, obstruction of the larger sinus can produce the picture of severe intracranial pressure.   I have seen 2 such cases already this year.   Bilateral obstruction, of which I have experience of only one case, seems to be disastrous, since if the patient survives he must suffer intolerable headache and near-blindness.

(5) Papillœdema, if it occurs at all, is relatively late, and implies obstruction of a large sinus.   It is rare and unnecessary to the diagnosis.

(6) Lateral sinus thrombosis is the commonest cause of otogenic cerebellar abscess and superior petrosal thrombosis is a significant factor in temporal lobe abscess.

(7) There never was any need for *routine* ligation of the jugular vein and there is even less to-day.   If one can get comfortably below a clot, say at the knee, what point is there in increasing the patient's troubles by the addition of a neck operation.   Almost as many cases died from central spread as from peripheral diffusion, and in any event the surgeon has to trust *the* clot, or *a* clot, somewhere.

(8) In a large experience of cavernous sinus thrombosis, which includes 4 cases arising from quinsy, I have never seen a case of sphenoidal origin.   The textbooks and teachers of my youth rather stressed the sphenoid.   In pre-sulphonamide days I only saw one recovery from a cavernous sinus thrombosis.   Medical treatment nowadays largely prevents the development of the complication and saves most of the few which do occur.

A case of cavernous sinus involvement, one of a series of 6 successive recoveries (Reid and McGuckin, 1946) was that of a child aged 3.   She recovered with some surgery, much sulphonamide (48 grams in the first eleven days) and a great deal more of skilled medical and nursing management.   The details include lateral sinus thrombosis, superior-petrosal thrombosis, bilateral cavernous involvement, paralysis of the VI nerve, pneumonia, whooping-cough, primary pulmonary tuberculous complex and finally food poisoning.   She survived all of these.   Penicillin was not then available.

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Mr. Maxwell Ellis said that thrombosis was a mechanism of repair localizing the lesion to the blood vessel and protecting the body from something worse.   It was a perfectly natural process and should not be interfered with.   He firmly believed that it was a great mistake to open the lateral sinus, since this merely resulted in the formation of further clots.   In fact, whatever was done to a blood vessel, ligaturing, dividing or opening and packing, ended in the production of a clot.   Trying to get rid of the clot was therefore irrational   unless—and this was the real point—unless the clot were infected.   A sterile clot was a pretty firm thing and emboli from it of no practical significance.   Obviously septic emboli were a very different matter, but did the opening up of an infected clot really prevent their occurrence?   Sterilization of the clot, rather than the impossible task of trying to remove it, was the therapeutic objective.

He thought that nowadays they had a very much better weapon than the surgeon's knife, and that was chemotherapy.   In a bad case it was unjustifiable to wait several days until the sensitivity had been established.   In his own experience almost all cases were sensitive to a combination of sulpha drugs together with penicillin and streptomycin and it was his practice to give these drugs at the outset.   If the sensitivity could be identified later, obviously so much the better.   Mr. Crabtree had said that the over-prolonged use of antibiotics might be responsible for lateral sinus thrombosis.   That was certainly a possibility.   But it was also possible that the use of chemotherapy might have saved the patient from some fulminating disaster for which a thrombosis was a reasonable substitute; anyhow, it was *post hoc, ergo propter hoc*.   His own experience of these cases was entirely in the sulphon-amide and antibiotic era, and he had a strong preference for antibiotics as opposed to the surgeon's knife, although he always cleared out the infected mastoid cells and bone.   There seemed to have been a vast number of these cortical mastoid operations done in Birmingham since 1950.   He thought he personally saw about two acute mastoids a year and he wondered whether these cortical mastoidectomies had been a conservative attempt to get rid of a chronic disease or whether they were done for acute disease.   In his cases of lateral sinus thrombosis only 3 out of 15 had occurred in acute infections.

His only reasons therefore for opening the lateral sinus were (1) to drain a clot which had already broken down and liquefied, and was therefore really an abscess, and (2) to evacuate a clot which had remained infected in spite of chemotherapy.   Applying these rigid indica-

tions, he had only opened the lateral sinus four times. He had never yet found it necessary to tie the internal jugular vein; he agreed entirely with what had been said about that. If a case came up suffering from some form of pyæmia, it might be rational to tie the vein as a preliminary. He had never done it, but he mentioned it as a possible preliminary means of treatment before the patient was saturated with antibiotics.

Mr. E. D. D. Davis said that he was interested in cases of lateral sinus thrombosis. He had kept notes of 27 lateral sinus patients and 10 cavernous sinus during twenty-five years. He had only 1 case in 1939 and another in 1940 but there had been a considerable reduction in the number of cases before the introduction of the antibiotics. Better feeding, housing, hygiene and more skilled medical and surgical treatment has reduced the number of cases of sepsis of all kinds. How could penicillin be expected to have any effect on a perisinus or an apical mastoid abscess? How could penicillin be expected to have any action when the blood supply to the thrombosed area is cut off? A lateral sinus thrombosis arose from an acute osteomyelitis of the mastoid. It used to occur commonly after scarlet fever or measles. The commonest cause was a cholesteatoma with an acute attack of suppuration. The patient was very ill and a threatened or suspected thrombosis demanded immediate operation.

He would like to ask Mr. Radley-Smith whether he had any experience of the operations for opening and draining the cavernous sinus?

Mr. P. E. Roland said that in chronic otitis media lateral sinus thrombosis was usually considered to be associated with an exacerbation of the infection. This exacerbation might not be obvious on examination of the tympanic membrane as experienced in 2 cases of sigmoid sinus thrombosis associated with cholesteatoma. Otoscopy in both showed attic perforations which were quite dry. He thought that antibiotic treatment at some earlier stage in the disease might have led to a cessation of the discharge while the disease progressed in the mastoid. With the ever-increasing use of antibiotics this experience was likely to become more common, and more importance should be placed on the history and the presence of an attic perforation than the finding of foul discharge.

Mr. R. F. J. Martin wished to make two points about the treatment of lateral sinus thrombosis. In most cases it was preferable to refrain from opening the sinuses provided that all the surrounding bone was meticulously removed; at the same time, where possible, blood was withdrawn from the sinuses for bacteriology and sensitivity tests in order to determine the most suitable antibiotic.

Tying the internal jugular vein was often useless and added to the risk of otitic hydrocephalus.

Mr. W. O. Lodge asked whether, in cases of septic thrombophlebitis of the sigmoid sinus, the speakers attached clinical significance to localized tenderness over the mastoid emissary vein.

When the cavernous sinus was infected, he had recently operated by the transantral route, locating the foramen rotundum in the same sagittal plane as the supra-orbital and submental foramina, and trepanning immediately medial to that. A cyathus (a Galenical measure of about 4·56 c.c.) of pus was evacuated from the venous sinus and associated cerebral abscess. The patient, a child age 6, survived; she was a little simple-minded afterwards but there was every confidence that she would eventually recover completely.

Mrs. F. Cavanagh described 2 cases of cavernous sinus thrombosis, secondary to ear infection. Both occurred in children and were associated with meningitis. In each case penicillin and heparin were given. The patients were lumbar punctured on several occasions. After a few days, when the general condition had improved, she opened the mastoids. Both made a complete recovery. This was several years ago and both are now fit and healthy.

Mr. E. J. Radley-Smith, in replying on the discussion, said that trauma was a possible cause of intracranial thrombosis. Undoubtedly trauma in the leg was a common cause of thrombophlebitis in the leg. On the other hand, one did not commonly see thrombophlebitis after head injury. Mr. McGuckin had raised the question of cavernous sinus from quinsy; he himself had seen it twice; it was a very definite cause.

On Mr. Davis's question concerning the approach to the cavernous sinus of Ballance, he had had no personal experience of that approach, but if one was going to approach the cavernous sinus he thought there was a better operation and that was the "pawnbroker"

operation of Stallard and Harvey Jackson, where one could get right across to the optic nerve, the second division of the V nerve below, and the inner wall of the orbit, leaving no deformity afterwards.

With respect to the electroencephalogram and the diagnosis of cerebral abscess, he agreed that cortical thrombophlebitis and cerebral abscess often co-existed. He and his associates had the opportunity a few years ago of correlating EEG localization of cerebral abscess with operation findings. They found that the EEG focus was commonly a good deal too far forward, or back. He regarded other methods of accurate localization of a cerebral abscess as far more reliable.

Mr. Norman Crabtree, who also replied, said that Mr. Maxwell Ellis had commented on the question of sensitivity for chemotherapy and antibiotics. He hoped he had made it clear in his opening paper that he was not suggesting that mastoid surgery should be delayed, but only that when the case first appeared cultures should be taken and every effort made to identify the organism and its antibiotic sensitivity. He had also asked about cortical mastoidectomy. The author said that the great majority of these cases were of acute mastoiditis rather than an attempt at conservative treatment for chronic infection. Tenderness over the mastoid emissary vein was found—to take up the point made by Mr. Lodge—but he regretted that he had not personally seen a sufficient number of thrombosis cases to know whether it was a reliable sign or not.

[*February* 4, 1955]

A DISCUSSION was held on Malignant Disease of the Middle Ear and Meatus. Papers were read by **Mr. J. W. S. Lindahl** and by **Mr. John Boland** and **Dr. Ralston Paterson.** These papers will be published in the *Journal of Laryngology and Otology.*

The following took part in the discussion: **Mr. W. A. Mill, The President, Mr. Maxwell Ellis, Dr. M. Lederman, Mr. R. Thomas, Professor F. C. Ormerod, Mr. Hector Thomas, Dr. Constance A. P. Wood, Mr. A. Mackenzie Ross, Mr. R. D. Owen** and **Mr. Henry Shaw.**

[*March* 3, 1955]

THE Dalby Memorial Lecture was given by **Mr. Terence Cawthorne:** his subject was **Otosclerosis.** This lecture will be published in the *Journal of Laryngology and Otology.*

[*March* 4, 1955]

A DISCUSSION was held on Radiology of the Temporal Bone. Papers were read by **Dr. Sölve Welin** (Malmö) and **Mr. W. I. Daggett.** A paper was also read by **Dr. T. V. I. Crichlow** who opened the discussion. These papers will be published in the *Journal of Laryngology and Otology.*

The following took part in the discussion: **The President, Professor F. C. Ormerod, Mr. R. F. J. Martin, Mr. Terence Cawthorne** and **Mr. R. D. Owen.**

Section of Odontology

President—C. BOWDLER HENRY, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

[*November* 22, 1954]

An Unusual Composite Odontome

By B. E. D. COOKE, F.D.S., M.R.C.S.Eng., L.R.C.P.Lond.

From the Department of Dental Medicine, Guy's Hospital

WHILE the fully calcified odontomes have received frequent attention in the literature, it is from a study of the less common, soft and partly calcified odontomes that most is learnt about the inductive influences of one type of tissue upon another. The case under discussion is probably a developmental anomaly involving epithelial and mesenchymal elements occurring after the odontogenic epithelium has lost the power of inducing dentine formation.

Clinical features.—Mr. S. H., aged 53, had noticed a firm swelling in $\overline{654|}$ region of the mandible since the extraction of his teeth fifteen years earlier. This swelling which had not noticeably enlarged over the years, was about 2 cm. long and 1 cm. wide. The intra-oral radiograph (Fig. 1) shows in the alveolus an oval thick radiopaque shadow
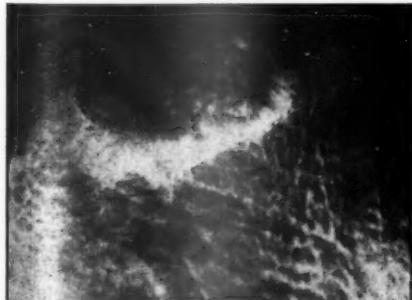
FIG. 1.—Intra-oral radiograph, $\overline{654|}$ region, showing a thick radiopaque shadow encircling a radiolucent area stippled with small opacities.
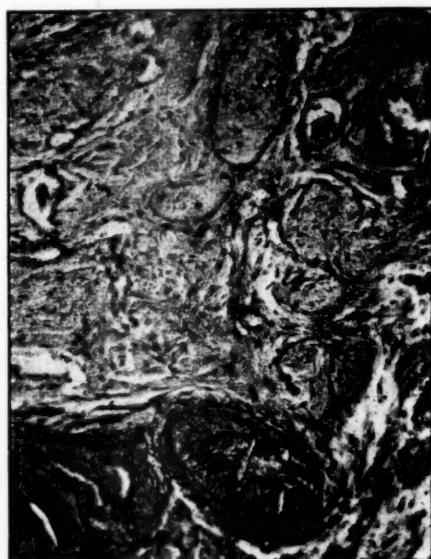
FIG. 2.—Showing coarse-fibred woven bone and cementum. Schmorl's picrothionin. ×83.

encircling a radiolucent area stippled with small opacities. Elsewhere the bone pattern is normal. The outer opaque margin is of the density of bone and has adjacent bony trabeculæ merging with it, while the enclosed radiopacities could represent woven bone or cementum.

Pathology.—Macroscopical examination of the specimen. Hard mass (1·5 cm. × 1·0 cm. diam. approx.) covered on one aspect by a strip of gum.

MAY

Histopathology.—Almost enclosed in a thick shell of lamellar bone is an area of fibrous connective tissue containing cementicles of all sizes and many epithelial strands and rests of a very inactive appearance. This shell of bone was incomplete under the well-keratinized stratified squamous gingival epithelium, and did not show any osteoclastic resorption or remodelling suggestive of an expanding lesion. Although a little coarse-fibred woven bone (Fig. 2) is present peripherally, most of the calcified globular nodules can be identified as cementum by the concentric arrangement of their trabeculæ, the fibrillar matrix, the finding of fewer enclosed cells than occur in bone, and the characteristic way in which it cracks on decalcification (Fig. 3). The intervening fibrous tissue is vascular, loose and, in places, undergoing a myxomatous degeneration. There are many epithelial cell nests scattered throughout the lesion but only one or two are actually adjacent to the cementicles (Fig. 4). Many of these epithelial cells are vacuolated, and twice their normal size, with the nucleus pushed to one margin. These inactive epithelial rests are often associated with the myxomatous areas.


FIG. 3.—Showing cementicles. H. and E. ×58.
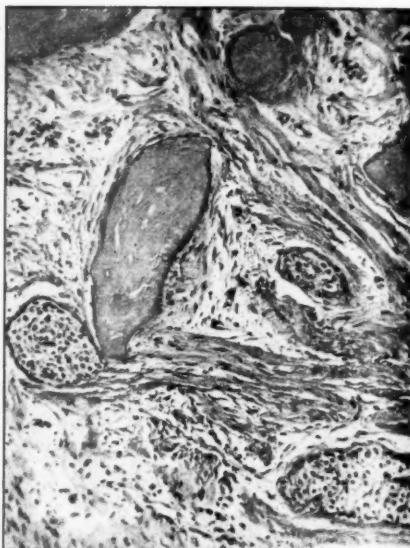
FIG. 4.—Showing cementicles and epithelial rests in loose fibrous connective tissue. Van Gieson. ×83.

DISCUSSION

This is a malformation of dental tissue involving epithelium and mesenchyme resulting in an admixture of fibrous tissue, epithelial rests and cementum. Cementum appears to have formed at about the same rate as normal cementum, and the long clinical history together with the inactive microscopical appearance of the lesion argues against its being the cementoblastic stage of a cementoma.

Thoma and Goldman (1946) in an excellent paper entitled "Odontogenic Tumours; a classification based on observation of the epithelial mesenchymal and mixed varieties", describe two types of mixed odontogenic tumours that are partly soft and partly calcified. The first is characterized by a soft epithelial component, a soft mesenchymal component and dentine, the second by a soft epithelial component and enamel, a soft mesenchymal component and both dentine and cementum. The present case forms a third group, a soft epithelial component, a soft mesenchymal component and cementum. Dentine did not form presumably because the original tooth in relation to it was completed.

Myxomatous degeneration is a marked feature of this case and Stafne and Parkhill (1947) found similar degeneration in a mass of fibrous tissue containing epithelial rests below the apex of an unerupted third molar in a girl aged 17. This could be regarded as an earlier stage of the same lesion, which if it had been left and the molar had completed its development, might have formed cementicles.

The epithelial rests are in the main not very closely associated with the cementicles, and are not likely to have induced the formation of the latter. It is not surprising that there is a little woven bone formation in the periphery of the lesion for the mesenchyme would contain undifferentiated cells capable of developing into osteoblasts as well as cementoblasts.

Thus this malformation of dental tissues is thought to have developed after the odontogenic epithelium had lost its power of inducing the formation of dentine while cementoblastic activity continued.

ACKNOWLEDGMENTS

I wish to thank Mr. F. Coker for kindly referring the specimen for histological examination, Professor M. A. Rushton for permission to publish this case and Mr. J. E. Hutchinson for the photomicrographs.

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[*January* 24, 1955]

Hyaline Bodies in the Epithelium of Dental Cysts

By MARTIN A. RUSHTON, M.D., F.D.S.

IN 9 cases in recent years, sections of dental or dentigerous cysts have been noted, in which the lining epithelium contains peculiar solid bodies, usually in isolated patches. This represents about 4% of sections of such cysts examined. The specimens concerned were from both sexes, from patients between 38 and 78 years of age, and from either jaw. The appearance must certainly have been noticed by many histologists but I have been unable to find that it has been described.

The bodies measure up to about 0·1 mm. in length and have some characteristic shapes which may occur separately or together. One of these is linear (Fig. 1), straight or curved

FIG. 1.—Linear bodies within the epithelial lining of a dental cyst. Cyst cavity above. Van Gieson's stain. ×334.

into various figures, often in a double strip as if an oval has been completely flattened with a little granular material at its centre, or like a hairpin. The bodies frequently seem to have

sustained several fractures and are clearly extremely brittle at some stage. Another appearance resembles broken-up pieces of plate. A third aspect is of circular or polycyclic agglomerations, sometimes laminated (Figs. 2, 3). The nuclei of epithelial cells are often closely apposed to their surfaces.
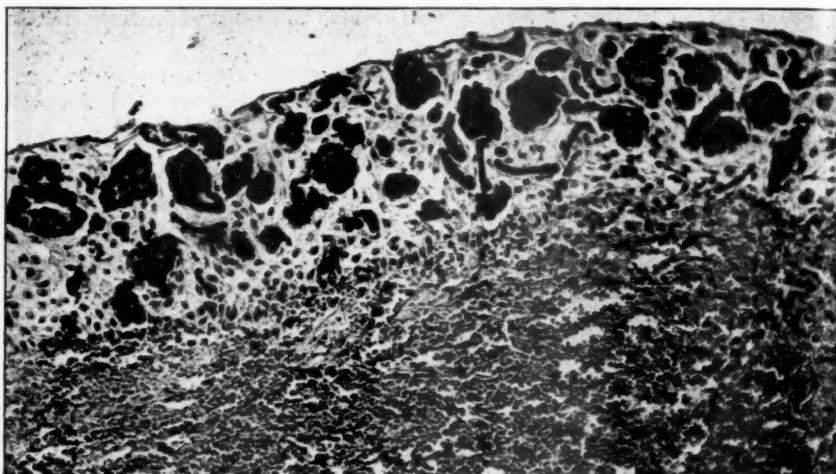

FIG. 2.—Both linear and polycyclic bodies in the cyst lining. Van Gieson's stain. ×130.

The bodies occur only in the epithelium or on its surface and are irregularly distributed. A few particles lie close to the basal layer but most lie away from this, and many are being shed into the cyst cavity. The extreme confusion of fragments often found and tears in the tissue may be partly connected with the collapse and contraction of the cyst wall when the fluid contents were released and the cyst wall was stripped out.

The linear forms may be found in the same pattern in several adjacent sections, so that they probably represent short sheets or flakes cut across and not rods. They appear to be the same as the plate forms but seen at a different angle. The circular or polycyclic bodies are bounded by one or more layers of this same clear material but their centre is different and granular.

The clear material resembles in appearance and liability to fracture the so-called keratinized layer of the epithelial attachment of a tooth (secondary cuticle of Gottlieb). It is eosinophil, Gram-negative, and gives a negative result with von Kossa's method for calcium and the periodic acid Schiff method for mucopolysaccharides. However, it gave a positive Prussian blue reaction varying from pale to strong, a diffuse coloration sometimes of different intensity in different layers of the same body. It also stained selectively with aldehyde fuchsin (Gomorri, 1950) after oxidation with permanganate, and either faintly or strongly without. According to Scott (1953) aldehyde fuchsin has an affinity for acid sulphur groups such as the sulphuric groups of sulphated mucopolysaccharides and the related sulphonic groups produced by the oxidation of cystine. In one specimen which also showed an unerupted tooth, the clear material coloured in the same manner as the secondary enamel cuticle, weakly before and strongly after oxidation, while the other enamel cuticles and remnant of enamel matrix stained only after oxidation. By the performic acid Schiff method (Pearse, 1951), the clear material was stained, but not in all places and not very deeply. The bodies exhibit either no birefringence or only an extremely low degree: the secondary dental cuticle which according to Cape and Kitchin (1930) is definitely birefringent and according to Orban (1953) shows marked birefringence, was only feebly birefringent in my preparations. The staining reactions have not been pursued further, but there seems a probability that the material in different places is not exactly the same, possibly undergoing changes which ultimately lead to a keratin or related substance.

The other material concerned is that which is enclosed inside the layers of clear material in the polycyclic bodies. This is usually of a granular nature and retains most dyes but not aldehyde fuchsin and does not give the Prussian blue reaction. Similar masses which had not become enclosed in a clear layer could be found. It was thought that they might perhaps
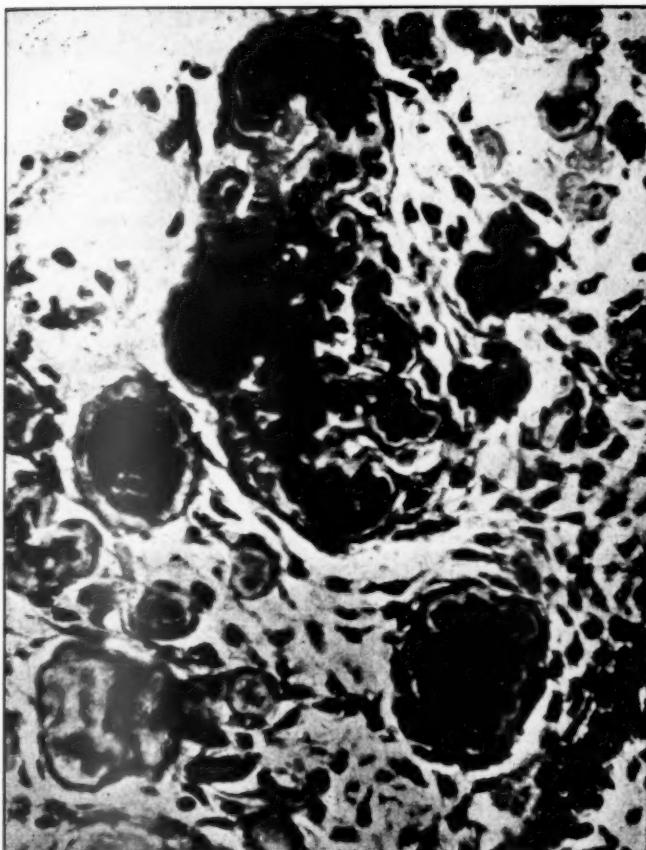
FIG. 3.—Enlarged view of polycyclic bodies to show clear surface layer.   Heidenhain's hæmatoxylin.   × 334.

represent masses of degenerating cellular material such as macrophages, which are present in abundance in the cyst walls and cavities.   It appeared as if the clear layers had been deposited successively around a granular material previously existing and that this may have been the result of contact with epithelial cells by which the material was surrounded, rather in the manner in which the secondary dental cuticle is applied to the cervical enamel and cementum.

If this be so, then the linear and plate-like bodies may represent the exercise of a similar function, possibly peculiar to epithelium of dental origin.

I am indebted to Mr. J. E. Hutchinson for making the histological preparations and photomicrographs.

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BOOK REVIEWS

Brain Mechanisms and Consciousness: A Symposium organized by the Council for International Organizations of Medical Sciences. Edited by J. F. Delafresnaye. (Pp. xvi + 556; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1954.

This is at least the third symposium upon its subject held within the past few years, this subject being the so-called "reticular activating system" of the brain-stem and its cephalic and caudal pathways and activities. When it is borne in mind that the subject also has its original literature in all the relevant journals, it will be seen how symposia multiply the presentations of a single topic and swell the bulk of the literature, and by sheer repetition seem to lend a reality to the subjects dealt with that is sometimes beyond their strictly factual merits. This symposium has all the qualities of its kind: more stress on theory and less on experimental detail. But the final discussion perhaps justifies the volume, for it makes clear that there are marked divergencies of view as to the facts of observation and as to the deductions to be drawn from them.

The morphology of the reticular activating system remains in a measure unclear. In the brain-stem this "integrating system", as it is for some of its exponents, does not correspond with the reticular formation of the anatomists, while in the thalamus its nuclei are not generally agreed, and its thalamo-cortical extensions remain in the realm of speculation. Nevertheless, that there is a mechanism in the central core of the brain-stem which by its activity maintains the cerebral cortex in a state in which it is capable of functioning in association with consciousness, is clear.

Acting caudally, it may prove to have a comparable activating function in respect of motor activities, but not that attributed to it by Magoun, since his hypothesis is based upon views of the role of the pyramidal system that are no longer valid.

For Magoun, however, this general function of "activation" is all that he claims for the system. Penfield and Jasper, on the other hand, regard the reticular formation of the brain-stem as the highest level of integration within the nervous system, and as the place to which are referred all sensory impulses reaching the cortex, and to which all efferent impulses from the cortex are sent. It is a master system within the brain and, by implication, seems to be the seat of consciousness.

This view of a basal and brain-stem seat of consciousness haunted the imaginations of the early Victorian neurophysiologists, and Penfield's hypothesis, though clothed in more modern terminology, is the authentic intellectual descendant of these speculations. The final chapter of the symposium reveals what a weight of authoritative opinion there is against this raising of Jackson's "lowest level mechanism" to the status of a "highest level mechanism".

Textbook of the Rheumatic Diseases. Edited by W. S. C. Copeman, O.B.E., M.D., F.R.C.P. 2nd edition. (Pp. viii + 754; 464 illustrations, some in full colour. 52s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

The second edition of this book has been expanded; it now contains 70 more pages than the first edition. Although there is one chapter less, those remaining have been lengthened and much new material added. There is a new chapter on the adrenal hormones, the chapters on rheumatic fever and rheumatoid arthritis have been expanded; and there is now a section on rehabilitation. These additions are welcome and bring the book well up to date as due emphasis is given to other recent advances in knowledge. The main arthritic syndromes are presented fully, although it is surprising to find gonococcal arthritis so briefly dealt with while the rarer conditions receive particular attention and perhaps the chapter on the physical environment might have been condensed in a textbook such as this.

The chapters on "non-articular rheumatism" are perhaps less satisfactory. Various writers have contributed different chapters and since this is an admittedly controversial subject there are some obvious disagreements between them. The result must sometimes be confusing, particularly to students and non-specialist practitioners. For instance the part played by fatty herniations in causing pain in the back is emphasized in one chapter but stated to be rare in the next. Further, while the concept of fibrositis as meaning an inflammation of fibrous tissue is shown to be erroneous the term is still used throughout the book either as though it were a real entity or as "fibrositis" or as fibrositic pain. The term rheumatism is also over-used even though the dangers and difficulties of this are well known and indeed are pointed out in the chapter on statistics.

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Some omissions must be noted. The shoulder-hand syndrome and tennis elbow receive only passing notice and amyloid disease is not mentioned in the clinical chapter on rheumatoid arthritis.

Nevertheless the book gives a good general picture of the subject, the references to most chapters are complete and valuable and the production of the whole book leaves nothing to be desired. The figures and plates are very good, the radiographs particularly being clear and well presented.

Maladies des Os et des Articulations. By Stanislas de Sèze and Antoine Ryckewaert. (Pp. 1,218 + xvi; 391 illustrations. Fr. 9,300.) Paris: Éditions Médicales Flammarion. 1954.

This tremendous volume starts with thirty excellent illustrated pages on bone physiology and growth, followed by a review of radiological changes associated with early bone pathology of all types, and a very complete classification of known and unknown causes of bone disease. The next five hundred pages is devoted to an elaboration of this classification which ranges from microbic infection to bone changes due to endocrine disorders and tumours, ending with a fascinating account of some bone diseases of unknown origin.

Tuberculous disease of bone is given no more space than syphilitic and parasitic disorders, which seems a pity, having regard to its greater frequency.

Bone disease of congenital origin including the chondrodysplasias is very fully dealt with and so far as the reviewer's knowledge takes him nothing is omitted. Here again the illustrations, both photographic and radiographic, are of an exceptionally high order for a continental publication.

In this first section there is a most interesting chapter dealing with bony defects resulting from metal and other chemical poisons, mostly occupational hazards.

The reviewer must confess to finding himself bogged down in the chapter on bone pathology associated with endocrine disorders, but anyone with both an interest and knowledge of this important subject will find here a mass of well-documented facts. The chapter dealing with bony changes associated with dietary and vitamin deficiencies is one of the best in the book, and the bibliography is very complete.

One feels more space could have been given to post-traumatic bony changes, as this subject plays such an important part in orthopædic practice.

The last portion of this third of the book, dealing with the rarer bony diseases, many of unknown origin, is truly magnificent, and entitles the work to a place among the leading books of reference on this subject.

The next five hundred pages deal with joint pathology; joint physiology is briefly detailed, and as in previous sections, a pathological classification is given; slightly less forbidding than the previous one. The rheumatic disorders are fully documented and the many possible ætiological factors, such as maladaptation, terrains, heredity, &c., are detailed with animal experimentation, some of it a little horrifying.

Twenty closely packed pages are devoted to all forms of treatment of chronic polyarthritis. Tuberculous diseases of joints again receive no more and no less attention than the other rare conditions such as Reiter's syndrome. Arthritis affecting the hip, knee, hand, foot and spine are each given separate chapters with admirable accounts of all available forms of medical, chemical, thermal and surgical treatment. Gout is discussed *in extenso* through thirty pages. Presumably this disease is more prevalent in France than in this country.

The last two hundred pages deal with periarticular conditions such as painful bursæ about the shoulder-joint; the manifold ætiological factors causing sciatica are described with a wealth of detail verging on the prolix, but nothing, it seems, is omitted.

Cervico-brachial neuritides and the varying factors giving rise to them are clearly and fully classified with much detail while on the other hand more space might have been devoted to Dupuytren's contracture, and some of the more recent publications on this subject are not discussed.

Acroparæsthesia and other rare syndromes are briefly outlined.

To sum up, this is a formidable volume. Formidable in its presentation and its completeness. It is not a criticism to say that it is compiled rather with Teutonic thoroughness than Gallic flair. As a tome of reference it is of very general and practical value alike to the pathologist and physician as to the orthopædic surgeon. Here they will find whatever minutiæ may interest them and a tremendous bibliography to carry them further if they need.

Section of Urology

President—VICTOR W. DIX, F.R.C.S.

[*October* 28, 1954]

THE following cases and specimens were shown:

Testicle, Neurofibroma.—Mr. A. WILFRID ADAMS.

Treatment of Glands in Primary Neoplasms: (1) **Seminoma**. (2) **Carcinoma Penis**. (3) Carcinoma Scrotum.—Mr. NEVILLE STIDOLPH.

Segment of Bladder with Attached Loop of Isolated Ileum Resected Six Months after Ileocystoplasty.—Mr. ARTHUR JACOBS.

A Massive Calculus of the Bladder Around Nylon.—Mr. A. WILFRID ADAMS.

A massive calculus of the bladder (weight 220 grams) formed round nylon sutures in the patient, W. O., male, aged 72 years—one strand seen centre of sawn section. Five years before, he had open prostatectomy, and foul septic cystitis developed as years passed. Death followed shortly after suprapubic lithotomy 28.7.54, and post-mortem confirmed that it was attributable to the foregoing condition.

Tubercular Vesico-rectal Fistula.—Mr. C. I. MURPHIE.

Uretero-vesical Protrusions.—Mr. D. INNES WILLIAMS.

An Unusual Uretero-colic Fistula.—Mr. RICHARD A. MOGG.

Massive Hydronephrosis.—Mr. J. D. FERGUSSON.

Liposarcoma of the Kidney.—Mr. RICHARD A. MOGG.

An Unusual Ruptured Kidney.—Dr. G. T. TATE (introduced by Mr. HOWARD G. HANLEY).

Intermittent Hydronephrosis.—Mr. HOWARD G. HANLEY.

Parathyroid Tumour and Renal Calculus.—Mr. F. R. KILPATRICK.

[*November* 25, 1954]

DISCUSSION ON NON-SPECIFIC PROSTATITIS

Dr. Gustav Giertz (Lecturer in Urology, Karolinska Sjukhuset, Stockholm):

I shall give only a brief survey of a few of the problems concerning prostatitis that we have been especially interested in at the Karolinska Sjukhuset in Stockholm. Most of the work has been performed by my collaborators Doctor E. R. Romanus and Doctor C. Franksson and by the staff of the X-ray department under the guidance of Professor K. Lindblom.

The only urological clinic in Sweden is at the Karolinska Sjukhuset, so that the patients have mostly been referred to us for special investigation and treatment.

Examination.—In a rectal examination with the patient standing the vesicles are in a horizontal position forming a U open backwards. The finger must be moved backward and laterally to be able to grasp the tip of the vesicles. They are normally very movable and if one tries to palpate them by moving the finger upwards in the same plane as the prostate, the organ slides in front of the finger and one is unable to examine it. We have proved this by taking X-rays during the examination and with the vesicles filled with contrast material.

Urethrography.—Edling of our X-ray department has written a thesis (1945) about the technique of urethrography including studies during micturition. In 1952 Morales and Romanus published their extensive studies about urethrography with a highly viscous contrast medium—Umbradil Viscous U of Messrs. Astra, Ltd., Sweden. The viscosity has been increased to that of syrup by carboxymethylcellulose, which also decreased the osmotic irritation caused by the contrast preparation. The discomfort which may result in misleading contractions of the musculature is eliminated by the addition of the rapidly acting anæsthetic agent Xylocaine. The new preparation completely wets the mucous membrane surface, in other words a drop will spread entirely over the surface. For studies of the

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posterior urethra a special technique with active contraction of the pelvic floor was worked out. How well even small ducts can be shown is seen from Fig. 1. A lot of small paraurethral ducts and cavities in the prostate and vesicles are filled.
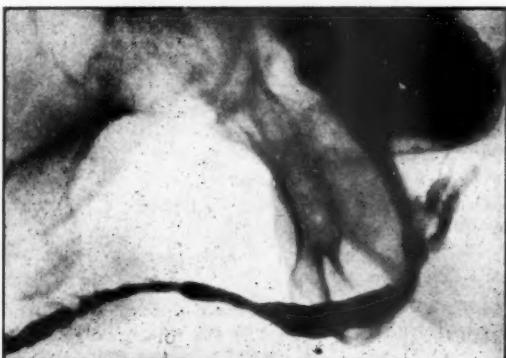

FIG. 1.—Urethrography with highly viscous contrast medium.

Cowper's glands.—Fig. 2 shows some of the complications which may occur in a case of prostatitis, a stricture and in micturition a prestenotic dilatation of the posterior urethra with increasing filling of the ducts and cavities of the prostate. The most interesting detail in the picture, however, is the demonstration of the bulbo-urethral duct and gland, best filled during micturition. We think the infection of Cowper's glands is too often overlooked. The ducts pass for a few centimetres through the cavernous tissues of the urethral wall and


A   B
FIG. 2.—Urethrography in stricture of the urethra. A, Injection picture. B, Micturition picture.

a chronic infection of one or both of them will cause a sclerosis in the neighbourhood. In the case in Fig. 2 the cowperitis was probably the cause of the stricture and that is not an unusual finding. In an early acute stage there might on the picture be a deviation of the urethra caused by the swelling of the gland. In one case with such a deviation we found two years later, when the process was in a chronic stage, a contrast-filled dilated duct and a urethral stricture. A more effective treatment during the acute stage might have prevented the development of the stricture. In a few cases we have tried the surgical removal of the infected gland and duct.

Enlarged utricle.—An enlarged utricle may cause prostatic symptoms by retention and infection. On rectal examination the finding is mostly typical. With the utricle filled with secretion there is a soft bulging in the middle of the prostate. With stripping this disappears

more or less easily and when the utricle is empty a distinct central depression is felt which may reach the upper border of the prostate. In some cases the utricle can be filled by urethrography, in others we·have demonstrated it by urethroscopy and catheterization. We have operated upon these cases in different ways. In one case with a very big cyst, we performed a suprapubic operation making a wide opening between the cyst and the posterior urethra, in other cases we opened the utricle by performing a transurethral resection. Nowadays we mostly just cut through the utricle wall with a diathermy catheter.

Romanus has drawn our attention to the fact that patients with an enlarged utricle often have hæmospermia. In a series of 75 cases of hæmospermia two-thirds showed signs of chronic urogenital infection; there was, however, only one case of tuberculosis and none of carcinoma. Many had severe pathological changes in the seminal vesicles thus explaining the hæmospermia; in others, however, the bleeding source lay in the abnormally large utricle. Œstrogenic hormones cause metaplasia of the utricular mucous membrane and thus reduce the tendency towards hæmorrhage and secretion.

Prostatitis and nerve-root lesions.—Recent investigations by Franksson and Petersen have shown that in many cases of prostatitis we have also signs of neurogenic disturbances, nerve-root affections, such as herniated discs and fibrosis of root sheaths. First they studied the sensory innervation of the prostate. The sensibility of the mucous membrane of the prostatic urethra was tested, and further they passed needles 1 cm. into the prostatic tissue and in some cases coagulated the tissue by means of needles insulated except for the tip. In each case the patients localized the pains to the deep tissues behind the symphysis, the base of the scrotum, the perineum or radiating to the penis. When the vesicle end of the prostate was stimulated the patients felt the pain mostly higher up, sometimes immediately above the symphysis. On stimulation at the apex of the prostate the sensations predominated at the base of the scrotum and in the perineum. Radiation into the penis occurred especially on stimulation of the colliculus and adjacent tissues.

In some cases of prostatitis there are in addition to this typical prostatic pain, pain of radicular type and other signs of root involvement, paræsthesias, sensory impairment, muscle atrophy or positive Lasègue's test. It was considered that there might be a connexion between the prostatic symptoms and the neurogenic disturbances. We know from Attwater and others that prostatitis might be accompanied by a hypotonic bladder and by hypotonia of the prostate and seminal vesicles. In 22 cases with prostatic symptoms, studied by Franksson and Petersen, enlarged bladders were found in 14, and in the majority also the bladder pressure was lower than normal. Therefore, in some cases of prostatitis the infection may be only a secondary factor, the primary cause being the neurogenic hypotonia of the prostate and vesicles. The probability of hypotonic origin will be greater in the presence of an enlarged urinary bladder with low pressure. The presence of additional nerve-root symptoms will lend further weight to the diagnosis. It is evident that neurogenic disturbances in a relatively circumscribed area may affect both the sensory and the motor innervation of the prostate, vesicles and bladder. Since we started with this diagnostic work a few patients have been sent to our neurosurgical department and operated upon.

Prostatitis and pelvo-spondylitis ossificans.—Romanus (1953) has studied the importance of prostatitis as a focus in rheumatic diseases, especially in ankylosing spondylitis (morbus Bechterew-Marie-Strümpell), by him termed pelvo-spondylitis ossificans. The disease is an inflammatory process, which in the vast majority of cases starts in the sacro-iliac joints. It then attacks the spine usually in an ascending process which involves all the elements of the spine, the vertebral bodies, their processes, joints and intervertebral discs. This inflammation appears to be localized mainly in the paravertebral connective tissue, attacking the spinal column from the surface. In a series of 105 cases Romanus showed that the illness, in the great majority of cases, starts in connexion with an infection in the prostate and vesicles. This theory gives an explanation of the fact that the incidence of the disease among men is about nine times greater than among women and that it often starts at the age of 25. The anatomical conditions necessary for the spread of infection or toxic agents from the prostatic region exist via the lymphatic routes or the vertebral venous system of Batson to the sacro-iliac joints and then to the spine and pelvis. This explanation also fitted the few cases in which the cause was chronic infection in the distal portion of the intestine. The different incidence of pelvo-spondylitis ossificans in the two sexes seems therefore to be due to the differences in the frequency and localization of chronic foci of infection in the pelvis and the arrangement of their lymphatic and venous drainage.

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ROMANUS, E. R. (1953) Pelvo-spondylitis Ossificans in the Male and Genito-urinary Infection. Stockholm. (In: *Acta med. scand.,* Suppl. 280.)

Mr. F. P. Raper (Consultant Urologist, United Leeds Hospitals and Leeds "A" Group Hospitals):

This paper concerns 100 patients with prostatitis most of whom have been seen in the last two years. They had all been sent by their own doctors for a urological opinion but only very few had been sent with a provisional diagnosis of prostatitis. It is suggested that prostatitis is a common disease the diagnosis of which is often missed. It is hoped to show how the diagnosis has been made and what treatment, if any, has been given.

The patients to be reported here have shown few obvious causes for their prostatitis and, apart from one which followed an injection for hæmorrhoids and three who developed the disease following respectively a sore throat, a tooth extraction and boils on the lower abdominal wall, it has been impossible to discover a primary infection elsewhere in the body. No minute or comprehensive search of teeth or tonsils has been made, however. Only one patient had previously been treated for gonorrhœa and in any case the modern treatment should have greatly reduced the incidence of chronic prostatitis as a complication. Patients with prostatitis secondary to urethral stricture or due to foreign bodies or tuberculosis have not been included in this series. The histological examination of prostatic adenomata removed by operation frequently reveals the presence of small areas of inflammation and sometimes even small abscesses, the inflammatory changes being most marked on the urethral aspect of the gland if there has been previous treatment with an indwelling catheter but small abscesses may be found even when there has been no catheterization. It is possible that such abscesses are sometimes the precipitating cause of acute retention in a person with an already enlarged prostate and such may be suspected when general malaise and fever occur immediately prior to the onset of retention. Antibiotics will sometimes relieve the condition and prostatectomy is not always needed. Although small areas of prostatitis are very commonly found on histological examination, only those patients with *symptoms* of acute prostatitis have been included in the series to be described.

In this series of 100 patients, the youngest is 28 and the oldest 80 but most have been seen in the 40s and 50s. Although many were seen at a time when their diseases might be described as chronic, this tends to give a false impression, for if the history is carefully taken the majority of patients will be found to have an acute pyrexial illness as the onset of their disease. A characteristic history may be summed up in a patient's own words, "I had been in bed with 'flu and then got cystitis". The interval between the "flu" and the cystitis may be anything up to two weeks and then the patient will not mention the "flu" because he sees no connexion between it and his cystitis. In other patients the disturbance of micturition almost coincides with the onset of fever and the diagnosis of "flu" never enters the picture. The usual complaints are then fever with frequency, pain or difficulty in micturition often associated with a persistent severe low backache or occasionally perineal pain and sometimes initial or terminal hæmaturia. 70% of the patients had such initial symptoms.

The acute symptoms usually subside and most of the patients have been seen because of recurrence of their initial symptoms in a less severe form than in the original attack or because of persistence of one of the symptoms such as frequency, pain on micturition or dysuria. A few have been seen because of epididymitis or with a request for the investigation of hæmaturia or backache.

Examination

Usually the only abnormal clinical finding has been in the examination of the prostate and there may be many different findings according to the stage of the disease. In the quiescent stage the prostate is usually smaller than average, is often flat and sometimes nodular. Only one-half of the gland may be involved. In the acute phase there is not much difficulty in recognizing the tender, hot, swollen prostate but when the acute phase is subsiding it is not nearly so easy to make the diagnosis. Then the edge of the prostate, often apparently extending well beyond its normal limit, may be very firm, while the centre may be quite soft and the whole may be surprisingly free from tenderness. Two patients first seen during this phase were thought to have malignant prostates. Despite a very careful search, it has only once been possible to feel a distended seminal vesicle and this was in a patient with epididymitis.

The urine examination.—This has not usually helped to confirm the diagnosis nor has it been of assistance in choosing the appropriate antibiotic for treatment. A mid-stream specimen of urine has been collected at some time from these patients (Table I). Two-glass or three-glass specimens of urine have not been collected because this method of sampling does not fit easily into the present outpatient routine. In comparing specimens of urine passed before and after prostatic massage, the second specimen has often been found to contain large quantities of pus, debris and prostatic threads.

TABLE I.—MID-STREAM SPECIMENS OF URINE FROM 75 PATIENTS WITH PROSTATITIS

Pus cells: sterile	32
Normal	20
Pus cells and *B. coli*	9
Pus cells and *Staph. aureus* ..	6
B. coli	6
Pus cells and *Staph. albus* ..	2
	—
	75

Urethrograms.—These have not been used to any great extent for diagnosis but they may help to reveal the size of an abscess cavity.

Panendoscopy.—The final proof of the presence of the disease is to see pus coming from the prostatic ducts or abscess cavities and this can almost always be found if the prostatic urethra is carefully examined. In the quiescent stages the abnormalities are restricted to the prostatic urethra and the bladder has only been found to be inflamed when an acute prostatic abscess was present. The mucosa in the prostatic urethra is usually found to be red and rough and dilated duct openings are found in the floor of the urethra between the verumontanum and the bladder neck. The former itself sometimes has granulomatous tissue on its summit but in later stages of the disease may be smaller than normal. Pus can often be made to emerge from the dilated ducts and abscesses by pressing on the lateral lobes with the panendoscope or by pressing gently on the prostate via the rectum. It must be remembered that normal prostatic fluid is slightly turbid and must not be mistaken for pus.

Treatment

The best chance of curing the disease is to treat it in its earliest stages with adequate doses of an antibiotic such as Chloromycetin. Unfortunately it is not often recognized in the early stages. Undergraduate teaching must take some of the blame for this for patients with this disease are rarely admitted to hospital and the opportunity to teach about it does not often occur. Surgical textbooks normally used by students contain no clear description of the disease and frequently relate it only as a complication of gonorrhœa. It is desirable to attempt to cure the disease before much prostatic destruction has occurred for this is the only way to prevent recrudescence of infection and eventual bladder-neck fibrosis or prostatic calculus formation.

Once the disease has become established it is difficult to decide what is the most effective treatment, for the natural history of the disease is so variable that it is almost impossible to assess results. But it is logical to suggest that the persistently infected prostate causing symptoms should be treated like other localized infected tissue and either excised or at least adequately drained. This will necessitate some form or degree of prostatectomy and there are certain risks.

(1) Transurethral resection of infected tissue may wash organisms and pus into the blood stream with the irrigating fluid. This risk can be greatly minimized by operating only when there is adequate antibiotic already in circulation.

(2) There is a fear that prostatectomy in a young person may cause sterility either by injury to the ejaculatory ducts or by injury to the sphincter at the bladder neck. If only an infected part of the prostate requires removing, it is often possible to do this without damaging either of these structures.

13 patients in this series have had deliberate resection of infected prostatic tissue because of recurrent attacks of prostatitis. 2 other patients have had a similar resection but with the specific purpose of obtaining a specimen for histological examination. All 15 patients have been free from symptoms since operation but the length of follow-up is far too short to be of real value.

2 other patients who had large recognizable, fluctuant prostatic abscesses had these abscesses drained by a transurethral incision and wide opening of the abscess. Perineal incisions for such abscesses have not been used. Both patients are free from symptoms.

14 patients have had deliberate prostatectomies because difficulty in micturition had persisted after the acute symptoms of prostatitis had been controlled. These patients were all older than the average for the group. 4 had transurethral resections and 10 had retropubic prostatectomies, and all have had good results.

In none of the 29 patients operated on with known prostatic infection were there any post-operative complications due to spread of the infection.

No total prostatectomies have been done.

Of the patients who had operations, 2 who had definite prostatic abscesses (1 containing 7 oz. of pus) were found to have an unsuspected prostatic carcinoma when the excised prostatic tissue was examined histologically.

About one-third of the patients have had operative treatment and the remaining two-

thirds have had conservative treatment. This has amounted to treatment with a sulphon-amide or some antibiotic for up to three weeks. Almost all these patients are free from symptoms but no attempt has been made to verify the absence of infection by prostatic massage.

Prostatic massage as a therapeutic measure has been used for only one patient and as no relief of symptoms and no reduction of pus in the prostatic fluid has occurred after six weeks' treatment, the patient has been advised to have a transurethral prostatectomy.

Finally two particular types of prostatitis must be mentioned.

(1) *Granulomatous prostatitis.*—Only one example of this has occurred in this series. He gave a characteristic history of an acute prostatic infection which subsided and then recurred within a month, on the second occasion causing retention of urine. He had a transurethral prostatectomy, the histological appearances of the lesion being shown in Fig. 1. There was
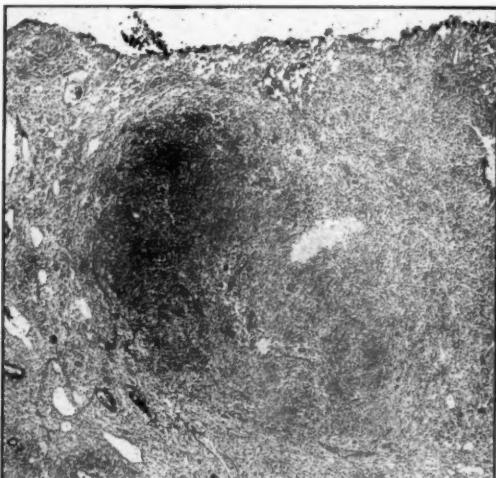

FIG. 1A.—Low-power view ($\times 30$) of a piece of prostate removed by transurethral resection showing one of the foci of granulomatous prostatitis containing several giant cells.
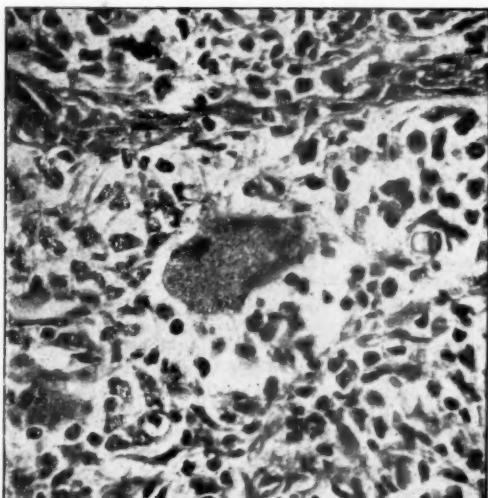

FIG. 1B.—High-power view ($\times 373$) of one of the foreign body type giant cells seen in Fig. 1A.

no evidence of tuberculosis in the upper urinary tract and no tubercle bacilli were found in the urine.

(2) *Allergic prostatitis.*—Two examples of this were reported by Stewart *et al.* (1954). They quoted 4 other cases which had previously been reported. The history is characteristic for it may be suspected if acute retention of urine suddenly develops in a true allergic asthmatic subject. Other symptoms of allergy may be present such as urticaria. The patients reported all had a routine prostatectomy and only the histological appearances led to the diagnosis. The characteristic histological feature is the presence of large numbers of eosinophilic pus cells in foci scattered throughout the prostate. They may lie in prostatic ducts or amongst the adenomatous and fibromuscular tissue. Professor Stewart suggests that in such a patient prostatic massage should produce a fluid loaded with eosinophilic pus cells, and antihistamines might be a useful line of treatment. These cases must be very rare.

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Mr. A. H. Harkness:

Non-gonococcal prostatitis (I prefer the term "non-gonococcal" to "non-specific") can be venereal or non-venereal in origin. It should be remembered, however, that some cases described as non-venereal may well have followed a mild, untreated and unregarded abacterial urethritis which has been venereally acquired.

Venereal causes.—In the pre-chemotherapy era cases of subacute and acute prostatitis due to non-gonococcal organisms were frequently observed during treatment for gonorrhœa as well as for non-gonococcal urethritis. Usually the determining factor in precipitating this complication was inefficient local treatment. A non-gonococcal urethritis with or without prostatitis is now by no means infrequent after treatment of gonorrhœa with penicillin, but in such cases it is usually due to a non-gonococcal infective agent having been present in mixed infection with the gonococcus before treatment was started.

Nowadays in some cases of *subacute abacterial urethritis* a symptomless prostatitis can be diagnosed. Thorough rectal examination rarely reveals anything abnormal in the consistency of the gland but smears of the expressed secretion sometimes show clumps of leucocytes.

Chronic inflammation of the gland is claimed by some to be the most frequent cause of relapse after apparent cure, but many of these so-called relapses are really reinfections.

The incidence of prostatitis is not high, though some workers think otherwise. Ambrose (1954) of the United States, considers that the cellular content of the prostatic fluid generally parallels that of the urethral exudate. I know of no work carried out on the histopathology of this disease. Nevertheless the infiltrations in the anterior urethra appear to lie superficially on the epithelial lining of the mucous membrane with little or no involvement of the subepithelial connective tissue or glands of Littré. I have never seen peri-urethral indurations or abscesses, and strictures, though frequently seen by aero-urethroscopy, never show any diminution in the calibre of the urethra sufficient to prevent the passing of a full-size instrument even over long periods of observation. In cases of symptomless prostatitis there can develop—though rarely—a subacute and slowly resolving epididymitis which sometimes is wrongly considered to be tuberculous. Inflammation of the gland has never, in my experience, progressed to cause acute signs and symptoms either with or without abscess formation.

The disease seems to be due either to a virus or to a pleuropneumonia-like organism. It is worth noting, however, that the protozoon *Trichomonas vaginalis* is present in some cases resistant to treatment in both urethral and prostatic secretions. In 14 of the 60 cases in a recent series in which the flagellate was present in the prostatic secretions there was a long delay in resolution. In other cases it was, in all probability, leading a commensal existence similar to that described by Hoare (1952) for entamœbæ in amœbiasis. It would appear that the incidence of a trichomonad prostatitis has increased considerably since the introduction of antibiotic therapy, and this may be a serious problem for the future.

Acute abacterial urethritis of venereal origin is a much rarer disease than the subacute variety. Its symptoms of posterior infection are always severe though it is sometimes difficult to determine whether the inflammation of the bladder is also accompanied by inflammation of the prostate since palpation often reveals what appears to be a perfectly normal gland: the exudate expressed may come either from it or from the infected bladder. Residual subacute infection occasionally persists. In 7 of my cases cystoscopy had been performed by surgical colleagues during the disease's acute phase before the commencement

of treatment and in all of them the generalized cystitis was similar to that in abacterial pyuria.

It should be remembered that the blood-borne complications of the so-called Reiter's disease may arise during the course of both acute and subacute abacterial urethritis.

Both varieties of the disease react favourably to the antibiotics derived from the lower-grade fungi, but penicillin and the sulphonamides, in my hands at least, are ineffective. In a recent series of 1,328 cases oxytetracycline was effective in 85% of those in which it was employed; tetracycline in 84%; chlortetracycline in 63%; erythromycin in 50%; streptomycin in 40%; chloramphenicol in 34%. The dosage for erythromycin was 300 mg. six-hourly for four to six days, but for all the other drugs it was 0·5 grams six-hourly for the same period. The drugs probably attack the infective agent from the urine as well as from the blood stream so my patients are therefore advised to cut down their fluid intake by half during the course but to pass urine frequently, however small the amount, in order to enhance the drugs' local action. If the "L" organism is the infective agent then the effectiveness of Aureomycin, erythromycin and chloramphenicol is probably due to their local action. The blood levels obtained with most of the drugs (except erythromycin which is lower) are 10 micrograms per millilitre but only with oxytetracycline and tetracycline (the most effective drugs) is the concentration more than enough to inhibit the growth of this organism. Resistant subacute infections of the gland react more favourably to twice-daily urethrovesical irrigations with warm and weak solutions than to prostatic massage or diathermy.

I have made no mention of a *bacterial (non-gonococcal) urethritis of venereal origin*. Primary infections of this kind, though frequently described in the past, are, in my opinion, extremely rare. Thorough cleansing of the meatus should always precede the taking of specimens and if organisms are then found in the secretions the infection is more likely to be of non-venereal origin. This is especially so in infections due to staphylococci and coliform bacilli. I have never seen a primary ascending urethritis of venereal origin in the male which has been due to B. coli, a surprising fact when one considers that there is a high incidence of non-gonococcal urethritis among active homosexuals.

Non-venereal causes of prostatic inflammation may be summarized as follows: (1) Direct spread of urinary infection; (2) trauma; (3) focal infection; (4) pre-existing diseases of the gland; (5) infestations with protozoa, metazoa and fungi.

(1) *Direct spread of urinary infection*.—It is noteworthy that the prostatic ducts and also the urethral mucous membrane show a remarkable natural resistance to many urinary infections. A non-gonococcal urethral discharge may indeed be the only symptom of a lesion of the prostate or disease of the upper urinary tract. Such inflammation of the prostate is the most frequent cause of a descending urethritis. Co-existing obstruction of the lower tract predisposes to an infection of the gland and in such cases the inflammation is more likely to progress to abscess formation.

(2) *Trauma*.—A not infrequent cause of inflammation of the gland is injury from chemical, mechanical or thermal agents. The organisms responsible may be exogenous and due to one or more of the saprophytic flora of the fossa navicularis becoming pathogenic in damaged tissue. They may also be those (usually B. coli or Staph. aureus) admitted to the urethra on foreign bodies. Endogenous organisms in a previously infected urine may also be responsible.

Prophylactic syringing of the urethra with strong solutions sometimes traumatizes the posterior urethra and subacute inflammation of the gland may supervene. The mechanical trauma of urethral instrumentation (especially in cases in which there is infected urine), such as that caused by undue force in the passing of sounds, the insertion into the urethra of foreign bodies, and the indwelling catheter may also be responsible. It should be noted that injury to the gland by instrumentation may be insignificant and cause no discomfort to the patient. I have seen several cases in which severe involvement of the gland has followed the injection of hæmorrhoids where the anterior pile has been the target of injection and where the technique has been faulty. In such cases the prostatic sheath is perforated thus allowing organisms, usually coliform in type, to take a footing in tissue destroyed by the injected fluid.

(3) *Focal infection*.—Inflammation of the gland may arise from foci of infection in teeth, tonsils, nasal sinuses and boils. I have also treated recurring attacks of B. coli prostatitis which were considered to be due to organisms absorbed from the large intestine. No other focus of infection could be detected and attacks invariably coincided with constipation.

In all such cases as the above (though perhaps not the B. coli infections from the intestine) there must be an at least transient bacteriæmia to enable the organisms to reach the genital tract, but the constitutional disturbance of a systemic reaction is lacking. It has been shown by Okell and Elliott (1935) in their investigations in bacteriæmia in oral sepsis that

organisms may enter the blood stream irrespective of operative procedures. A transient bacteriæmia, similar to that previously described by Barrington and Wright (1930) following urethral trauma, was observed after extraction of teeth with gum disease. Indeed the mere rocking of the teeth induced bacteriæmia. It is therefore reasonable to assume that a bacteriæmia also occurs in boils and other sites of focal infection, but to my knowledge no investigation similar to those mentioned has as yet been carried out.

Mode of spread.—Infection of the prostate may be direct from the blood stream, but it is more likely that organisms infect the gland after passing through the kidneys with or without production of a renal carbuncle. I have not had a case where both were present at the same time. The teeth and tonsils are frequently blamed as sources of prostatic infection, but accurate diagnosis in such cases is extremely difficult. I know of no case in which organisms in both primary and secondary focus have been identified by bacteriophage typing. On the other hand I have seen quite a large number of cases of prostatic inflammation due to *Staph. aureus*, many progressing to abscess formation, that have occurred during or just after an attack of boils.

(4) *Pre-existing local diseases of gland.*—Calculi and benign or malignant enlargement are pre-existing conditions that may be associated with inflammation of the gland. In pre-chemotherapy days many cases of resistant infection were due to prostatic calculi which, in most cases, could only be detected by X-ray. Their incidence has lessened considerably in recent years, due no doubt, to the more efficient drugs now available for treatment of infections of the urogenital tract.

Benign enlargement and, sometimes, malignant disease are associated with inflammation of the gland and I have seen a metastatic abscess in a prostate affected by senile enlargement.

(5) *Infestation with protozoa, metazoa and fungi.*—Prostatic inflammation due to protozoa, metazoa and fungi may be primary or superimposed on previous inflammation. I have already referred to infestations of the prostate with *T. vaginalis* admitted to the urethra through venereal contact. Another protozoon, *E. histolytica*, is also sometimes found in the prostatic secretions as in a case I saw with Hoare and Murgatroyd (1948). This protozoon may gain access to the urinary tract not only by way of the external urinary meatus but also through the sinus of a rectovesical fistula resulting from amœbic ulceration of the intestine. Trichomonads do not penetrate the lining of the prostatic ducts, although biopsy of amœbic ulcers shows that they do reach the deeper tissues.

Redewill (1949) reported a case in which scrapings from the posterior urethra revealed ova of a small nematode, *Strongyloides stercoralis*. Goldsmith also states that hyperplasia from bilharzia infection may also occur in the prostate and gives rise to an egg-containing discharge. There are 13 cases on record of primary hydatid cysts of the prostate.

Mycotic inflammations of the gland are now extremely rare, and many of the cases previously reported were, in fact, due to faulty sterilization of instruments.

Diagnosis.—The diagnosis of prostatitis is sometimes extremely difficult and, as already stated, a symptomless urethral discharge is frequently the only sign of disease. The urine may be clear with threads in the first glass only and may give no indication of involvement of the posterior urethra.

In acute prostatitis, however, the diagnosis is usually easy as there is either a tender one-sided swelling or a generalized enlargement of the whole gland associated with urinary symptoms and constitutional disturbance. It is often difficult to decide whether the condition has progressed to abscess formation, but when this is so the constitutional disturbance becomes more marked and there is more likely to be retention of urine. Acute inflammations of the diaphragmatic glands of Cowper, especially in cases in which there is retention of urine, may be mistaken for acute inflammation of the prostate unless bi-digital rectal examination has been carried out, but this is a procedure usually omitted by urologists.

In subacute inflammation of the gland rectal examination often, as already stated, reveals no obvious palpable change, but there may be indurated or boggy areas in one or both lobes. It may be difficult to determine whether swellings of the gland are inflammatory and due to pyogenic organisms or tubercle bacilli, or whether they are caused by calculi or early malignant disease. A clear and sterile urine is more likely to be associated with malignancy. X-ray is usually necessary for the detection of prostatic calculi. Microscopic and cultural examination of secretion expressed from the gland should be carried out, 8 to 12 pus cells to a 1/12th field or scattered clumps of pus cells being regarded as abnormal.

Symptoms of subacute involvement of the gland.—As already stated there may be no symptoms referable to the prostate, but a detailed history sometimes reveals a mild frequency and dysuria. Nervous and apprehensive patients often have symptoms referable to the genitalia, the most frequent complaints being pain in the inguinal regions, perineum, testicles, penis and inner side of thighs. On investigation in some of these cases there is definite involvement of the gland, this being especially so in cases of recurrent attacks due

to *B. coli*, but in many it is impossible to detect any abnormality. I wish I could believe that the above-mentioned pains were always due to inflammation of the gland, and I certainly disagree with treatment by massaging the gland for indeterminate periods.

Treatment.—The general principles of treatment, such as rest and the avoidance of trauma, alcohol and sexual excitement, should be observed. Sulphonamide or antibiotic therapy will often modify profoundly the course of the disease. The choice of drug is indicated by sensitivity tests carried out on the organism or organisms isolated in the urine and prostatic secretions. It must be remembered, however, that in a certain number of cases relapse after apparent cure is inevitable unless the mechanical efficiency of the urinary tract has been restored by surgery. The treatment of prostatitis due to descending infection is, of course, that of the underlying pathological condition. It should be remembered that urethral stricture is a not infrequent sequela of certain types of traumatic urethritis associated with prostatic inflammation, also of urethritis and prostatitis due to *Myco. tuberculosis*. In such cases dilatations should be carried out after subsidence of acute inflammation. Here again in cases of non-venereal origin which are resistant to sulphonamide or antibiotic therapy urethro-vesical irrigations are, in my hands, more efficacious than massage of the gland or diathermy.

Fever therapy sometimes effects a rapid cure in cases resistant to the treatments already described.

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Mr. H. P. Winsbury-White:

Romanus (1953) had shown that prostatitis was often responsible not only for adolescent sacro-iliac disease, but for arthritis generally.

Mr. Raper had mentioned the frequency of so-called influenza in these cases. One very commonly discovered that the influenza could quite easily have been a prostatic infection because the patient ultimately admitted that he had had a temperature without respiratory tract symptoms which culminated in the cystitis.

Mr. Raper had also spoken of the difficulty in interpreting a rectal examination in prostatitis. A prostate would sometimes feel completely normal but with the urethroscope prostatic infection would be observed. American writers had pointed out that prostatic smears could not always be relied on in diagnosing prostatitis. The speaker felt that there was no more reliable method in doubtful cases than using the urethroscope.

In his experience the proportion of the granulomatous type of prostatitis was larger than Mr. Raper had suggested. The granulomata commonly seen in the prostatic sinuses were evidence of badly draining prostatic ducts. An excellent method of treatment was to fulgurate them.

Injection for hæmorrhoids could suddenly precipitate symptoms indicating acute bladder-neck infections. A patient once described to him how within a quarter of an hour of injecting for hæmorrhoids he had very acute frequency and discomfort on passing water. He supposed that this was due to either the close venous or lymphatic connexion between the two areas.

A certain type of case was found in quite young men who often complained of renal pain for which no renal cause could be found, but prostatic infection in a mild and chronic form could account for renal pain of a persisting nature. The connexion was clearly shown when the renal symptoms disappeared as a result of treatment of the prostate.

REFERENCE

ROMANUS, E. R. (1953) Pelvo-spondylitis Ossificans in the Male and Genito-urinary Infection. Stockholm. (In: *Acta med. scand.*, Suppl. 280.)

Mr. John Swinney said that chronic prostatitis was difficult to treat. A great variety of organisms undoubtedly existed in this condition and no single antibiotic was likely to be effective. This had also been found to be the case clinically. He was, therefore, inclined to agree with Mr. Raper that the treatment of chronic prostatitis must be mechanical,

either by prostatic massage or by removal of diseased tissue by transurethral resection of the prostate. Even when the chronically inflamed gland contained calculi, transurethral resection was an effective form of treatment.

Mr. **A. W. Badenoch** said that this was an extremely difficult condition. His own cases fell into three main groups: (1) no symptoms, many signs; (2) limited symptoms, certain signs; (3) many symptoms, no signs. The people in the first group, had lots of signs, obvious pus and threads in the urine but they did not complain of the prostate at all, though they must have had prostatitis. The second group complained of symptoms and had pus and organisms in the urine. He thought they had to be thoroughly investigated and he had been most interested in Dr. Giertz's observations. He was quite sure that they had got to carry out Dr. Harkness's very extensive bacteriological investigations before deciding upon particular lines of treatment.

Two lines of treatment were available: (1) medical, by bactericidal therapeutics or antibiotics, and (2) mechanical, either by draining the foci of infection by transurethral resection or incision, or even in some cases, by total prostatectomy. It was obvious that in many cases there was a profound psychological effect of a depressive character and this was especially so in the third group of cases which were the most troublesome of all. They were those who had symptoms including pain in the perineum, in both testicles, and in the adductor regions, and yet nothing could be found wrong with the prostate other than a little tenderness and there was no evidence of infection. He thought the condition was some form of prostatic congestion and referred to such a case as an idio-prostato-centric. All sorts of treatments were given—courses of prostatic massage, stilbœstrol, testosterone and antibiotics—usually without effect. He had had one case sent him recently with the opinion that a radical prostatectomy should be done, and he had seen one man who by degrees had lost both epididymes and testes.

Mr. **D. T. H. Paine** said that he had himself been guilty of causing a prostatitis quite unwittingly following treatment for hæmorrhoids carried out with the greatest care, and he had recently missed a swelling in the perineum due to cowperitis. He desired to ask whether any of the speakers had any experience of injecting the prostate with antibiotics along the lines suggested in 1950 by Dr. Hatch and his colleagues in Minnesota (Hatch, W. E. (1950) *J. Urol.*, **64**, 763).

Mr. **Raper** said that he had no experience of injecting the prostate with antibiotics.

Mr. **A. Wilfrid Adams** said that it was interesting to find that eosinophilic prostatitis was evidently a genuine source of prostatic disturbance, and its occurrence might not be so rare as was supposed. Prostatism and asthma being by no means a rare combination, were some of these cases possibly allergic?

His pathologist colleague—Dr. A. L. Taylor—had told him (23.11.54) that antral and other respiratory mucosa sometimes show histological findings of allergic manifestations, exact replicas of Stewart's two cases.

Had any member present had a report in which the histologist had found eosinophilic foci, "abscesses" and giant cells in the prostate? The difficulty was that, as far as he knew, no one, scarcely, save Professor M. J. Stewart (Stewart, *et al.*, 1954) had ever seen the phenomenon histologically! He had begun to feel that calculi might cause prostatitis, for, unlike Mr. Raper, he was finding quite an appreciable incidence of them in the middle-aged coming with sharp attacks of clinical prostatitis. Did calculi provoke infective trouble or vice versa? He wished to ask Mr. Raper what he did in this chronic prostatic process, so-called "prostatitis"; and also his treatment for ordinary acute prostatic abscess.

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STEWART, M. J., WRAY, S., and HALL, M. (1954) *J. Path. Bact.*, **67**, 423.

Mr. **Raper** replied that as to allergic causes, in a series of approximately 200 prostatic cases a year for ten years allergy had been encountered to his knowledge only twice. It was a most striking thing when it was seen. In one of these cases there was acute retention and the prostate was removed two weeks later, and eosinophilia was present. As for the incidence of stone in these cases of prostatitis, he saw one such case the previous week with a stone in one of the prostatic ducts. He had treated only 2 cases by incising an abscess in the prostate perurethrally.

Asked what degree of mobility was obtained after prostatic massage or what number of pus cells remained, Mr. Raper said that they had never counted the number of pus cells in the urine. The normal prostatic fluid did look a little turbid if one watched the prostatic urethra while doing prostatic massage, but it was nothing like pus. Pus under these circumstances was quite easily recognizable as pus.

Dr. Harkness wondered whether in some of the cases described by Mr. Raper the disease had been acquired venereally. If this was so a mid-stream specimen would be misleading as the first gush of urine would carry the secretions in both the anterior and posterior urethra.

Mr. Raper replied that the mid-stream specimens were the routine mid-stream specimens taken when the patient went into the ward. This disease seemed to him to be much more common now than it was five years ago.

Mr. H. G. Hanley taking up this last point, said that he saw quite a number of young National Service men at Millbank Hospital, and he was quite sure that many more of them than formerly complained of pain in the perineum with frequency of micturition. The incidence had increased even within the last two years.

It was not generally realized that this could be a disease of very young men and he showed a slide illustrating prostatic concretions in a boy soldier age 17½ years.

[*February* 24, 1955]

THE following Cases and Specimens were shown:

Massive Relatively Benign Adenocarcinoma of Kidney.—Mr. HENRY CLARKE.

Papilloma of a Calyx Treated by Partial Nephrectomy.—Mr. THOMAS MOORE.

Partial Nephrectomy for Calculus (Two Cases).—Mr. A. G. RUTTER (introduced by Mr. R. H. O. B. ROBINSON).

Congenital Renal Abnormalities Presenting as Acute Appendicitis (Two Cases).—Mr. MARCO CAINE.

An Unusual Renal Carbuncle.—Lt.-Col. R. S. HUNT (introduced by Mr. HOWARD G. HANLEY).

Ureteritis Cystica.—Mr. RICHARD E. SHAW.

X-rays Illustrating Ureteric Reflux After Treatment of Ureterocele.—Mr. B. H. PAGE.

Cutaneous Tuberculous Ulcer of Unusual Origin.—Mr. R. A. MOGG.

Surgical Cloaca of Forty Years' Duration.—Mr. THOMAS MOORE.

Non-specific Inflammatory Mass in Front of Pubes at Root of Penis.—Mr. A. CAVENDISH-